

Reperfusion Therapies for Acute Ischemic Stroke: An Update

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Abstract: Acute ischemic stroke is a major cause of morbidity and mortality in developed countries. Intravenous thrombolysis with tissue plasminogen activator (tPA) within 4.5 hours of symptoms onset significantly improves clinical outcomes in patients with acute ischemic stroke. This narrow window for treatment leads to a small proportion of eligible patients to be treated. Intravenous or intra-arterial trials, combined intravenous/intra-arterial trials, and newer devices to mechanically remove the clot from intracranial arteries have been investigated or are currently being explored to increase patient eligibility and to improve arterial recanalization and clinical outcome. New retrievable stent-based devices offer higher revascularization rates with shorter time to recanalization and are now generally preferred to first generation thrombectomy devices such as Merci Retriever or Penumbra System. These devices have been shown to be effective for opening up occluded vessels in the brain but its efficacy for improving outcomes in patients with acute stroke has not yet been demonstrated in a randomized clinical trial. We summarize the results of the major systemic thrombolytic trials and the latest trials employing different endovascular approaches to ischemic stroke.

Keywords: Endovascular treatment, ischemic stroke, mechanical thrombectomy, stent-retriever, thrombolysis, tPA.

1. INTRODUCTION

Stroke represents the third leading cause of death in industrialized nations, after myocardial infarction and cancer, and the single most common reason for permanent disability [1]. A new optimism emerged after the advent of intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA, Alteplase) and, since then, stroke treatment has dramatically changed.

Intravenous (IV) thrombolysis with tissue plasminogen activator (tPA, alteplase) is the standard of care in the treatment of acute ischemic stroke in current clinical practice and the extension of the time window up to 4.5 hours after symptoms onset has been already approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) agency and included in European and American guidelines recommendations [2]. Despite iv tPA for stroke has become widely used in different countries since 1996, its use has several limitations such as short therapeutic window, low arterial recanalization rate, risk of major bleeding, moderate effect on non-selected patients and several exclusion criteria and contraindications leading to a low proportion of treated patients [3]. All these facts have contributed, over the last decade, to develop and study new thrombolytic drugs, new routes of administration, longer treatment windows of treatment and different mechanical devices to locally remove the clot.

Clinical outcome in ischemic stroke has been shown to be strongly linked to revascularization in numerous

independent studies [4-6]. A meta-analysis of more than fifty studies evaluating spontaneous or therapeutic arterial recanalization demonstrated a strong correlation between arterial recanalization and good prognosis [5]. Another key point that influences acute ischemic stroke outcome is the timing to recanalization. Randomized clinical trials with IV [7, 8] and intra-arterial [9] tPA have established that good clinical outcome after successful recanalization is time-dependent. However, thrombolytic therapy in longer therapeutic windows has been associated with improved outcomes when reperfusion/recanalization occurs when patient selection is based on mismatch concept using multimodal neuroimaging [10, 11].

Therefore, clinical and experimental research in acute ischemic stroke is continuously providing new strategies of acute management using pharmacological or interventional endovascular approaches and promoting the use of multimodal neuroimaging techniques as a treatment-selection tool. This article provides a comprehensive review of intravenous thrombolytic treatment and endovascular therapy in acute ischemic stroke based on the largest prospective studies and randomized clinical trials published to date (Table 1).

2. INTRAVENOUS THROMBOLYSIS IN PATIENTS WITHIN 4.5 HOURS OF SYMPTOMS ONSET

The National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator clinical trial demonstrated for the first time substantial benefit from the use of IV tPA in patients with acute ischemic stroke within 3 hours of the onset of stroke symptoms. In this study, patients treated with tPA were more likely to have a favorable neurological outcome at 90 days (OR 1.7; 95 % CI, 1.2-2.6;

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Table 1. Baseline stroke severity and outcome variables in the main endovascular and intravenous thrombolytic trials.

	n	NIHSS basal	Successful recanalization (%) (TIMI 2-3)	mRS 0-2 at day 90 (%)	90-day mortality (%)	Sich (%)
Endovascular treatment						
PROACT II [38]	121	17	66	40	25	10
MELT [39]	57	14	74	49	5	9
IMS [42]	62	18	56	43	16	6
IMS-II [43]	55	19	58	46	16	10
MERCI [46]	141	20	48 */60	28	44	8
Multi MERCI [47]	164	19	55 */68	36	34	10
Penumbra [53]	125	18	82	25	33	11
Trevo [66]	60	18	89	57	22	5
Solitaire [65]	141	18	85	55	20	4
SWIFT [67]						
Solitaire	58	-	68	58	17	2
MERCI	55	-	30	33	38	11
IMS-III [70]	434	17	-	40.8	19.1	6.2
SYNTHESIS [71]	181	13	-	42	14.4	6
MR RESCUE [72]	64	17	67	18.7	18.7	4
Intravenous thrombolysis						
Pooling analysis of IV tPA trials within 6 hours (tPA) [8]	1391	11	NA	49	13	5-9**
Control groups						
PROACT II (control) [38]	59	17	18	25	27	2
MELT (control) [39]	57	14	NA	39	3.5	2
Pooling analysis of IV tPA trials within 6 hours (placebo) [8]	1384	11	NA	44	15	1.1**
IMS-III [70]	222	16	-	38.7	21.6	5.9
SYNTHESIS [71]	181	13	-	46.4	9.9	6
MR RESCUE [72]	54	18	-	20.4	24.1	3.7

sICH : symptomatic intracerebral hemorrhage; * Device alone; **Parenchymal hematoma type II. tPA : tissue plasminogen activator, mRS : modified Rankin Scale ; NIHSS : National Institutes of Health Stroke Scale.

$p=0.008$). Compared to controls, tPA recipients had a 32 % relative increase in the likelihood of minimal or no disability with a 10-fold increase (6.4 % vs 0.6 %) in symptomatic intracerebral hemorrhage (sICH) [7]. Despite four other phase III clinical trials with tPA showed no positive results and failed in demonstrating the benefit of tPA a pooled analysis of the first 6 IV tPA trials (ECASS 1, ECASS 2, ATLANTIS A, ATLANTIS B, NINDS 1 and NINDS 2) confirmed the benefit of tPA up to 3 hours and suggested a potential benefit beyond 3 hours for some patients [8].

After its approval in Europe, The Safe Implementation of Thrombolysis in Stroke-Monitoring Study, SITS-MOST, indicated that, overall, routine clinical use of tPA within 3

hours of stroke onset is safe and effective out of randomized clinical trials [12]. In addition, the randomized clinical trial ECASS III showed a modest but clear benefit in terms of favorable outcomes for IV tPA in the 3 to 4.5-hour window as compared to placebo [13]. The results from ECASS III are in consistency with the previously stated time dependency on the effect of IV tPA. In the 3-4.5-hour window of ECASS III, fourteen patients were needed to be treated in order to achieve one additional favorable outcome as compared to 8 patients in the 0-3.0 hour window from the NINDS trial. The SITS-international Stroke Treatment Registry (SITS-ISTR) is a prospective, multinational, internet-based registry of unselected patients who are given IV tPA thrombolysis for

acute stroke in accordance with broadly accepted guidelines [14]. The SITS-ISTR investigators compared the outcomes of patients who received full dose IV rt-PA between 3-4.5 hours (n=664) versus within 0-3 hours (n=11,865) after ischemic stroke onset in clinical practice. The median time from symptoms onset to treatment was 195 minutes and 140 minutes, respectively. There was no difference in the main outcomes between the two groups even after adjusting for clinical trial prognostic variables. In agreement with the findings from the pooled analysis of the previous IV rt-PA trials [8], ECASS III and SITS-ISTR did not raise any safety concerns about IV thrombolysis at its later time window regardless of the lack of advanced imaging modalities to exclude presumed high-risk patients.

Importantly, beyond 4.5 hours from stroke onset, no net therapeutic benefit has been demonstrated and a meta-analysis of clinical trials with alteplase, including data from ECASS III and EPITHET, suggest an increased risk of mortality (OR 1.49, 95 % CI, 1.00-2.21) when alteplase is given in the 4.5 to 6 hours window from symptoms onset [15].

European license of IV tPA treatment has several restrictions on its use which have been adopted from the inclusion and exclusion criteria used in the randomized clinical trials. In many circumstances no evidence-based data are available and recommendations are based on expert judgments. Some of these restrictions are not considered by the United States and Canadian license and Stroke Guidelines. Of particular relevance because of their frequency are treating patients aged 80 years or older and those with prior stroke and concomitant diabetes. Recent data from the prospective registry SITS-ISTR (Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Registry) and the virtual archive of international clinical trials (VISTA) showed that, despite a worse outcome in patients >80 years compared with younger, thrombolytic therapy with IV tPA is associated with better functional outcome in both age groups [16-18]. In the international and multicentre Third International Stroke Trial (IST-3), 3035 patients within 6 hours of symptoms onset were allocated to 0.9mg/Kg intravenous tPA or to control. More than half of the patients included (53%) were over 80 years. The study concluded that thrombolysis within 6 hours improves functional outcome and the benefit do not seem to be diminished in elderly patients. So, these results should, therefore, encourage clinicians to consider thrombolytic treatment for patients aged over 80 years [19].

With respect to treating patients who had the combination of previous stroke and diabetes mellitus, although blood glucose levels > 180 mg/dl are associated with poor outcome and sHIC [20], functional outcome in alteplase-treated patients is better than in controls among diabetics, patients with prior stroke or with the coexistence of both factors [21].

Currently, tPA is the only approved drug that can lead to recanalization of occluded vessels and restore brain circulation before irreversible damage has happened in order to improve clinical outcome of patients treated at any age and in the presence of factors risk such as diabetes and previous stroke.

3. INTRAVENOUS THROMBOLYSIS IN PATIENTS WITH SALVAGEABLE TISSUE SELECTED BY MULTIMODAL NEUROIMAGING

There is growing evidence to support the notion of selecting patients for reperfusion therapy on the basis of brain tissue status as opposed to time from stroke onset. Three distinct regions can be identified in the ischemic brain according to the severity of hypoperfusion: (1) brain that is non-functional and irreversibly damaged (infarct core); (2) potentially salvageable hypoperfused brain that is functionally impaired but structurally intact and is destined to undergo infarction in the absence of reperfusion (penumbra); (3) hypoperfused brain that is both functionally and structurally intact and will not undergo infarction even in the absence of reperfusion (benign oligemia) [22, 23]. The hypothesis states that the higher is the mismatch between the infarct core and the penumbral tissue the higher will be the benefit from reperfusion regardless of how much time has elapsed since stroke onset. Multimodal Magnetic Resonance Imaging (MRI) allows, through the diffusion and perfusion sequence, establish those areas of brain tissue in which there is an alteration of cerebral blood flow (perfusion weighted imaging-PWI) without irreversible damage to the brain parenchyma (diffusion weighted imaging-DWI). Multiple retrospective clinical studies support the use of multimodal MRI to select patients eligible for thrombolytic therapy beyond three hours after onset of symptoms [24-26]. An MRI perfusion study demonstrated that as many as 70-80 % of the patients with proximal arterial occlusion may have a significant mismatch as far as 9 to 24 hours post stroke onset [27]. These studies imply that the therapeutic window may be protracted in selected cases and this constitutes the rationale for multimodal imaging selection.

Although the role of multimodal CT perfusion study in detection of ischemic tissue at risk is recognized, its value for selecting eligible patients for thrombolysis in longer time windows is controversial. The use of this technique for thrombolysis selection patients was associated with better functional outcomes (adjusted OR 2.88, 95 % CI, 1.50-5.52) compared with simple CT scan, mainly in patients treated after 3 hours [28].

Two main strategies applying imaging selection to clinical trials have been adopted. In the first one, all patients are treated regardless of their pretreatment perfusion pattern. This approach has been used in the DWI Evolution for Understanding Stroke Etiology (DEFUSE) [29] and Echoplanar Imaging Thrombolysis Evaluation (EPITHET) [30] trials and tests the hypothesis that patients with mismatch patterns will respond to treatment while those without mismatch patterns will not. The second approach uses perfusion imaging in order to only select patients with favorable mismatch patterns. This approach has been employed in the Desmoteplase in Acute Stroke (DIAS) and Dose Escalation of Desmoteplase (DEDAS) studies [31, 32].

The pooled analysis of the two phase II dose-finding randomized trials of IV desmoteplase within 3-9 hours of ischemic stroke onset in patients with DWI/PWI mismatch on MRI showed very promising results. The phase III DIAS-2 trial, however, did not confirm the benefit of this

treatment strategy [33]. The failure of DIAS-2 was largely attributed to the high response rate in the placebo group that was presumably related to the mild strokes and low proximal Middle Cerebral Artery (MCA) occlusions rate enrolled in the study. These factors reduced the potential to detect any desmoteplase effect. The ongoing DIAS-3 and DIAS-4 trials are no longer based on the mismatch concept. In these trials, ischemic stroke patients with proximal arterial occlusion or high-grade stenosis on MRI or CTA and a baseline NIHSS score of 4-24 are randomized to receive either 90µg/kg desmoteplase or placebo within 3-9 hours after the onset of stroke symptoms and should definitely elucidate if thrombolysis with IV desmoteplase up to 9 hours is safe and effective (ClinicalTrials.gov Identifier: NCT00790920).

The DEFUSE study was a prospective multicenter study in which 74 consecutive stroke patients were treated with IV rt-PA 3 to 6 hours after symptom onset [29]. Brain MRI was performed immediately before and 3 to 6 hours after treatment. Early reperfusion was associated with favorable clinical response in patients with a DWI/PWI mismatch (OR, 5.4; $p=0.039$). Conversely, patients with no identifiable mismatch did not appear to benefit from early reperfusion. Moreover, early reperfusion was associated with fatal ICH in patients with a “Malignant” profile defined as a baseline DWI lesion ≥ 100 ml and/or a PWI lesion ≥ 100 ml with ≥ 8 seconds of T_{max} delay [34]. The authors concluded that baseline MRI could identify patient subgroups that are likely to benefit from reperfusion therapies as well as subgroups that are unlikely to benefit or may be harmed by it.

While the aforementioned studies have failed to show a definite benefit for multimodal imaging-based IV thrombolysis at late time windows, they have demonstrated the overall safety of this approach with sICH rates equal or lower than what has been seen with non-contrast CT-based IV thrombolysis within the 0-3 hour window. Although delayed treatment according to mismatch selection cannot be widely recommended as part of routine care, new prospective phase III trials are running ongoing to validate the mismatch selection paradigm. The Extra time for Thrombolysis in Emergency Neurological Deficits (EXTEND) (ClinicalTrials.gov Identifier: NCT00887328) and the European Cooperative Acute Stroke Study-4 (ECASS-4) trials will select patients with MRI mismatch and a 4.5- to 9-hour time window by an automated online estimation of penumbra by the RAPID program, whereas The Imaging-based thrombolysis Trial in Acute Ischemic Stroke-II (ITAIS-II) is a prospective, blinded, controlled study that aims to study the safety and efficacy of multiparametric CT-based IV thrombolysis within 3 to 9 hours of stroke onset [35]. To test the safety of IV tPA in patients with unknown stroke onset or wake-up stroke, the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke trial (WAKE-UP) has already started (ClinicalTrials.gov Identifier: NCT01525290). This is a randomised, double-blind, placebo-controlled phase III clinical trial of MRI based thrombolysis in acute stroke patients with unknown time of symptoms onset and last time seen well >4.5 hours or patients with stroke symptoms recognized on awakening with a DWI-FLAIR mismatch pattern indicative of acute ischemic stroke less than 4.5 hours of age.

4. OTHER INTRAVENOUS THROMBOLYTIC AGENTS FOR ACUTE STROKE.

IV administration of tenecteplase dose escalation (0.1, 0.25, and 0.4 mg / kg) was compared with the standard dose of tPA 0.9 mg / kg in 112 patients with acute ischemic stroke within 3 hours after symptoms onset. The trial was prematurely stopped due to a lower clinical response and an increased risk of symptomatic hemorrhage in the 0.4 mg/kg dose of tenecteplase [36]. Later, an innovative design in a small sample of patients suggests that in patients with a proximal occlusion of the middle cerebral artery refractory to IV tPA treatment, a single bolus of tenecteplase (0.1 mg / kg) is safe and effective. Recanalization rate at 24 hours was 100 % and favorable outcome was observed in 69 % out of the 13 patients treated with both thrombolytic agents [37]. Recently, the results of a phase 2B, randomized clinical trial to compare the standard dose of alteplase with two different doses of tenecteplase (0.1 and 0.25 mg / kg) in the 6-hour window were published. CT perfusion and angiographic imaging was used to select eligible patients. Each treatment group comprised 25 patients. The higher dose of tenecteplase was superior to the lower dose and to alteplase for all efficacy outcomes. A phase 3 trial of tenecteplase versus alteplase in the time window that is currently approved for thrombolysis would be needed [38].

5. ENDOVASCULAR TREATMENT IN ACUTE ISCHEMIC STROKE

Compared with intravenous therapy, intra-arterial (IA) pharmacological therapy has the advantage of providing a higher concentration of lytic agent delivered to the clot target while minimizing the systemic exposure to drug and it has also the potential for greater efficacy with higher recanalization rates. This technique allows as well, the use of catheters to directly deliver a clot-disrupting or retrieval device to a thromboembolus that is occluding a cerebral artery. This last approach offers theoretical advantages over pharmacological thrombolysis, such as the rate and speed of recanalization, reduced risk of ICH and longer time window for use. However, mechanical approaches are particularly associated with greater technical difficulty, excessive trauma to the vasculature potentially leading to vasospasm, vessel dissection, perforation or rupture, and fragmented thrombus causing distal embolization into previously unaffected territories. Moreover, the disadvantages of endovascular treatment over intravenous, in general, include additional time required to initiate therapy and availability only at specialized centres.

Intra-arterial thrombolysis has been tested only in a few controlled trials including ischemic stroke patients with anterior circulation occlusions. There have been no published randomized controlled trials of endovascular therapy that have included basilar artery occlusions. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study demonstrated the safety and efficacy of IA thrombolysis in patients with an MCA occlusion [39]. One hundred and eighty subjects were randomized within 6 hours to treatment with IA pro-urokinase (UK) and IV heparin or IV heparin alone. Patients in the pro-UK group had a greater recanalization rate (66 % versus 18 %) and a better functional outcome at 3 months (40 versus 25 %) than patients in the control group.

Although sICH rate was greater in the pro-UK group (10 % versus 2 %), overall mortality rates were similar in the two treatment arms (25 % versus 27 %). The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) investigated IA urokinase versus placebo up to 6 hours after stroke onset in patients with a MCA occlusion [40]. The study was stopped when IV alteplase was approved in the 0 to 3-hour window but a substantial benefit was observed for the secondary end point of excellent (mRS 0-1 at 3 months) functional outcome (42.1 % versus 22.8 %). A meta-analysis of randomized, controlled trials evaluating 395 patients supported the benefit of IA thrombolysis for good (OR, 2.05; 95 %CI, 1.33-3.14) and excellent (OR, 2.14; 95 %CI, 1.31-3.51) outcomes [41].

Combined or bridging IV and IA pharmacological thrombolysis is a reperfusion strategy investigated in several non-controlled trials that has the benefit of faster initiation of IV treatment followed by rescue IA revascularization in patients who have not had a successful recanalization after IV treatment. The Emergency Management of Stroke Trial (EMS) and the Interventional Management of stroke Trial (IMS) demonstrated that the combined IV (0.6mg/kg)/ IA (up to 22 mg) tPA approach had similar rates of mortality and sICH compared with subjects of similar severity and age treated with IV tPA alone in the NINDS stroke trial, although no difference was observed in clinical outcome [42-44]. The IMS II study added the EKOS Micro-Infusion catheter to the protocol which uses acoustic streaming to increase fluid penetration, thus driving the thrombolytic agent into the thrombus [44]. The IMS II results showed a higher recanalization rate than in IMS I (73 % versus 56 %), but there were not statistically significant differences with respect to functional outcome at 3 months (46 % versus 43 %). A case-control study of 42 patients treated with bridging IV/IA tPA rescue therapy compared with 84 historical non-responder patients to IV tPA (persistent arterial occlusion 1 hour after tPA) showed that combined thrombolysis increases recanalization rate (45.2 % versus 18.1 % at 12

hours) and the likelihood of good outcome at 3 months (40 % versus 14.9 %) [45].

Merci Retriever was the first thrombectomy device used in a randomized clinical trial to evaluate the mechanical thrombectomy approach in the treatment of acute stroke. First patients treated as part of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) multicenter safety trial were published in 2004 [46]. After that, successive generations of the MERCI device have been reported in three prospective, single-arm, non-randomized multicenter studies with progressively better safety and outcome results [46-48]. This device is a spring-like device made of nitinol connected to the end of a wire with coil loops that is used with a microcatheter and a balloon-guided catheter (Fig. 1). MultiMERCi trial, using a newer-generation thrombectomy device (L5 Retriever), included patients within 8 hours of stroke onset who had either failed to respond to IV tPA or were ineligible for IV tPA. Recanalization was achieved in 55 % with the device alone, increasing to 68 % with combined mechanical and IA thrombolytic therapy, and sICH occurred in 9.8 % of patients. Overall, clinically significant procedural complications occurred in 5.5 % and mortality in 34 %. A favourable outcome (modified Rankin score of ≤ 2) was seen in 36 % of patients at 90 days. In a pooled analysis of the MERCI and Multi MERCI studies including 305 patients, successful recanalization was independently associated with good outcome (OR, 20.4; 95 % CI, 7.7 to 53.9) and reduced mortality (OR, 0.28; 95 % CI, 0.16 to 0.50) [49]. Importantly, the higher was the degree of recanalization the more frequent was favourable outcome, so that for each increase in TIMI grade, the odds of a good outcome increased 2.6-fold (95 % CI; 1.9 to 3.4) [50]. Previous IV tPA administration to mechanical embolectomy did not increase the risk of sICH (10.4 % versus 8.6 %) and procedure-related complications (4.2 % versus 6.6 %) compared to mechanical thrombectomy alone with a trend toward a higher revascularization rate (73 % versus 63 %) and less mortality (27.7 % versus 40.1 %) [51]. Although there was an association between time to

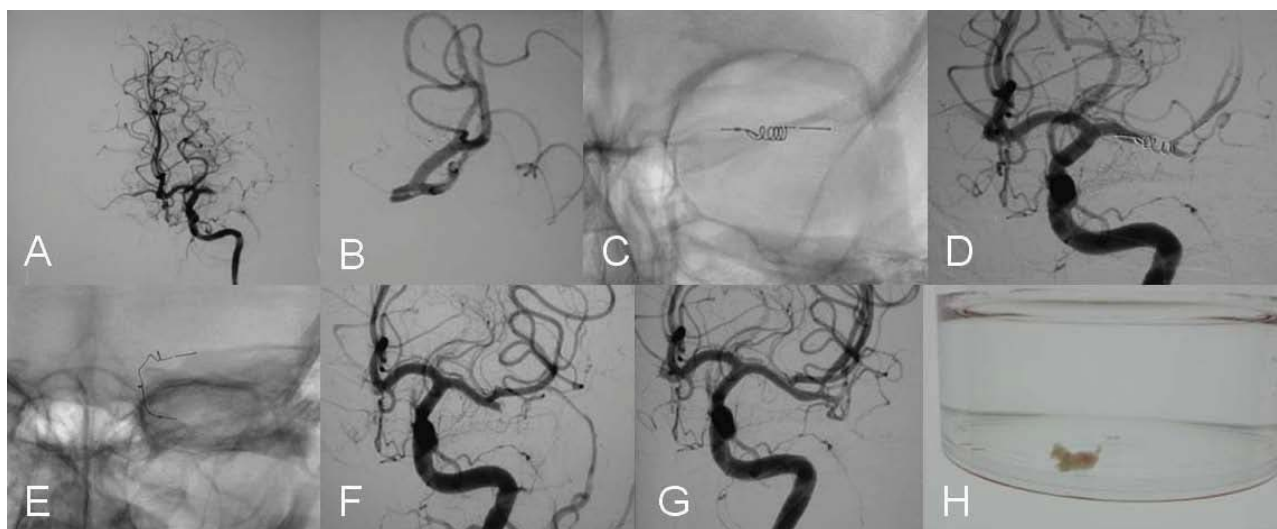


Fig. (1). (A) Initial angiogram shows an occlusion of left middle cerebral artery (MCA). (B) Microcatheter navigated beyond location of clot, demonstrating patent distal left MCA vascular bed. (C, D) Merci Retriever deployed distal to the occluding clot. (E) Merci Retriever is retracted back towards the carotid bifurcation, engaging the clot (F) After the first pass of the Merci Retriever, patency of the M1 segment of lenticulostriate arteries and of superior branch is achieved (G) Final angiogram demonstrates successful recanalization of the occluded vessel after the second pass of the Merci Retriever made in the lower branch. (H) Clot retrieved by the device.

reperfusion and clinical outcome after mechanical thrombectomy, its impact may not be as strong as IV thrombolysis, since a 40 % of late reperfused patients became independent [52].

The second tested device for the recanalization of occluded intracranial arteries in acute ischemic stroke was the Penumbra System. This device uses aspiration to remove the clot and open the vessels. The initial safety trial was published in 2008 [53] and, subsequently, was developed The Penumbra Pivotal Stroke Trial in 125 patients with cerebral ischemia up to 8-hours after symptoms onset, with neurological deficits defined by an NIHSS score ≥ 8 and an angiographically verified occlusion of a large intracranial vessel. [54]. The recanalization rate was 81.6 %, sICH occurred in 11.2 % and procedural events in 12.8 % of patients. All cause mortality was 32.8 % at 90 days with 25 % of patients achieving a modified Rankin score ≤ 2 . Similar to the MERCI and MultiMERCI trials, good outcome were more frequent (29 % versus 9 %) and mortality rate was lower (29 % versus 48 %) with successful compared with unsuccessful recanalization. Post-marketing experience of the Penumbra System has shown a safety profile of the device comparable to the one reported in the Pivotal trial with a trend to a better outcome (41 % versus 25 %) [55].

A systematic review and meta-analysis of 114 publications with 298 included patients treated with mechanical thrombectomy by diverse devices revealed a recanalization rate of 85 % and, in patients with accessible clots, 36 % of good outcome and 29 % of mortality. Compared with a historical matched cohort for sex, age and NIHSS, patients who received mechanical intervention were 14.8 times more likely to have a long-term good outcome [56]. A retrospective review of a prospective stroke database of endovascular

treatment has shown that manual aspiration throughout large catheters added to other thrombolytic modalities increases recanalization rates with equivalent safety profile compared with other mechanical revascularization methods [57].

Removable cerebral stents and clot retriever devices referred to as stentriever give a promising mechanical thrombectomy strategy. These devices avoid the need for strong antithrombotic medications that are used when an angioplasty with stenting is permanently deployed to achieve arterial revascularization, strategy that has been associated with an unacceptable risk of hemorrhagic complications [58]. Small case series and non controlled studies with different stent retriever devices (Solitaire™ AB/FR, Trevo®, Revive) have shown higher recanalization rates (around in 90% of patients), shorter time to recanalization and a trend to improved outcomes and safety profile compared to other endovascular approaches [59-67]. Moreover, SWIFT and Trevo2 trials showed the superiority of these new thrombectomy devices (stentriever) compared with the first thrombectomy device used in stroke (Merci Retriever) in terms of recanalization rate and good neurologic outcome at 90 days [68, 69]. Consequently, retrievable stent-based devices are a newer generation of mechanical thrombectomy devices that represent a valuable tool for endovascular treatment of acute stroke since complete thrombus removal is safely achieved in many patients, within short time, increasing the potential for improved outcomes compared to other reperfusion treatments (Fig. 2).

Despite more effective thrombectomy devices have been investigated in the last years, only three controlled clinical trials of endovascular treatment in acute ischemic stroke have been conducted. The recent results of the Interventional Management of Stroke III (IMS-III) [70], SYNTHESIS Ex-



Fig. (2). (A, B) Frontal basal angiogram showing a right terminal carotid artery occlusion. (C) Microcatheter navigated beyond location of clot, demonstrating patent distal right MCA vascular bed. (D) Magnified image showing Solitaire FR deployment at the occluded arterial segment through the thrombus. (E, F) A single pass of the Solitaire FR resulted in complete recanalization and reperfusion, as seen in the final arteriography. (G, H) Clot retrieved by the device.

pansion trial [71] and The Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) [72] have shown a lack of clinical benefit of endovascular therapy compared with standard medical therapy in patients with acute ischemic stroke. The IMS-III randomized patients treated with intravenous tPA within 3 hours after symptom onset to receive additional endovascular therapy or intravenous tPA alone. After 656 patients randomized, the study was halted due to futility according to the results of a pre-specified interim analysis. The proportion of participants with a modified Rankin score of 2 or less at 90 days did not differ significantly according to treatment (40.8% with endovascular therapy and 38.7% with intravenous tPA). The SYNTHESIS randomized patients within 4.5 hours after symptoms onset to endovascular therapy or intravenous tPA. Primary outcome was survival free of disability at 3 months (defined as a modified Rankin score 0 or 1). The results of this trial indicate that endovascular therapy is not superior to standard treatment with tPA showing that 30.4% patients in the endovascular-therapy group and 34.8% in the intravenous tPA group were alive without disability three months after stroke. In the MR RESCUE trial, patients within 8 hours after the onset of large-vessel, anterior-circulation strokes were randomly assigned to undergo mechanical embolectomy or receive standard care. Despite the trial was designed to study whether brain imaging can identify patients who are most likely to benefit from therapies for acute ischemic stroke, among all patients mean scores on the modified Rankin scale did not differ between embolectomy and standard care (3.9 vs 3.9, $p=0.99$) groups.

However, several limitations in the design and development of these previous trials that limit its generalizability have been reported [73, 74]. IMS-III and SYNTHESIS trials have only focused on intravenous tPA eligible patients, and therefore their results cannot be applied to intravenous tPA ineligible patients. Furthermore, some of the patients randomized did not have arterial occlusion or have lesions with no or low chances of benefiting from endovascular therapy. MR RESCUE trial included patients with large infarct cores at baseline and with very low rates of adequate early reperfusion. Moreover, the technology employed in the three trials is now obsolete. Only a minimal fraction of the patients in IMS-III trial were treated with stentrippers and almost half were treated only with intra-arterial tPA. First-generation embolectomy devices were the second most commonly used modality. In SYNTHESIS trial, about two thirds of the patients were treated with intra-arterial tPA and fragmentation of the thrombus with a micro guide wire and in MR RESCUE trial embolectomy was performed with the first-generation Merci or Penumbra devices. Overall, those reperfusion strategies do not reflect the current situation in which stent-retriever technology has demonstrated to achieve faster and more effective reperfusion compared to other strategies.

Despite endovascular treatment has not demonstrated a benefit in acute ischemic stroke in the three published trials, the safety of the treatment has not been questioned. Given the limitations displayed, endovascular revascularization remains justified in selected patients with a large vascular occlusion, salvageable brain and employing stent-retriever devices to achieve a fast and effective reperfusion. Thus

AHA/ASA 2013 guidelines recommend intra-arterial treatment of acute MCA occlusion within a 6-hour time window as an option (Class II-I, Level B) and in patients with contraindications to the use of IV thrombolysis, such as recent surgery (Class II, Level C). Another recommendation is that rescue intra-arterial fibrinolysis or mechanical thrombectomy approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis may be reasonable despite additional randomized trial data are needed (Class IIb, Level of Evidence B). The use of stent retrievers such as Solitaire FR and Trevo are preferred to coil retrievers such as Merci when mechanical thrombectomy is pursued (Class I; Level of Evidence A) [75].

The results from the ongoing randomized clinical trials such as REVASCAT (ClinicalTrials.gov Identifier: NCT01692379) [76], ESCAPE (ClinicalTrials.gov Identifier: NCT01778335) and SWIFT PRIME (ClinicalTrials.gov Identifier: NCT01657461) comparing best medical therapy and endovascular treatment with novel designs according to current technologies will be crucial to elucidate the true effect of endovascular treatment on clinical outcomes in patients with acute large intracranial artery occlusions.

CONCLUSIONS

Intravenous thrombolysis has demonstrated to be safe and effective up to 4.5 hours after symptoms onset, however the frequency of treated patients is still quite low as it is recanalization rate obtained. Endovascular approaches in the treatment of acute ischemic stroke offer higher recanalization rates compared with intravenous approach and has become a promising alternative for patients who are ineligible for intravenous thrombolysis or have failed in recanalizing the occluded artery. Nevertheless, its effectiveness in improving outcome has not been yet demonstrated in a randomized clinical trial. New randomized clinical trials with novel designs according to current technologies are necessary to elucidate the true effect of endovascular therapy for acute ischemic stroke on clinical outcomes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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DISCLOSURES

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