Treatment of acute ischemic stroke: from fibrinolysis to neurointervention

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Summary. Thrombolytic therapy with intravenous recombinant tissue plasminogen activator is well established as a beneficial treatment for patients presenting with acute ischemic stroke (AIS). The odds of a favorable clinical outcome (living independently) increase as the time between stroke onset and treatment with IV thrombolysis decreases. However, many patients present with a large clot burden that seldom responds to systemic fibrinolysis. Alternative options include new and emerging endovascular therapies that have recently proven effectiveness at restoring cerebral blood flow to the ischemic brain parenchyma. This review article will briefly outline some of the key evidence for intravenous thrombolysis as well as endovascular therapy for AIS.

Keywords: mechanical thrombolysis; stroke; thrombectomy; thrombolytic therapy; tissue plasminogen activator.

Introduction

Despite major advances in the field of stroke therapeutics in the past 2 decades, stroke remains a leading cause of disability and death worldwide [1]. Current therapies for acute ischemic stroke (AIS) aim to improve the long-term functional outcome of patients. To date, the only proven therapy for AIS is early recanalization [2], either with the administration of intravenous tissue plasminogen activator (IV-tPA) [3] or via endovascular interventions including intra-arterial thrombolysis [4], mechanical thrombectomy [5,6], or mechanaspiration [7]. Recent advances in endovascular therapy with the use of stent-trievers have shown effectiveness in recanalization of

occluded intracranial vessels and improvement of clinical outcomes [8–10]. Effective treatment of AIS requires the ability to rapidly assess and image patients, and optimally select patients for either treatment modality based on well-established eligibility criteria. In this article, we will briefly summarize the main evidence for the reperfusion therapies in AIS, encompassing the widely used intravenous fibrinolysis and the newer endovascular approaches.

IV Thrombolysis in AIS

The use of IV-tPA is a well-established standard of care for patients presenting with AIS within the first 4.5 h from symptom onset [3,11–13]. Moreover, the evidence for the use of IV-tPA is endorsed by several large organizations including: the American Heart Association/American Stroke Association, the Canadian Stroke Consortium, and the American Academy of Neurology (published guidelines available online).

Initially, the safety of IV-tPA was demonstrated in open-label, dose escalation studies showing that doses of less than 0.95 mg kg^{-1} were relatively safe and resulted in early neurological improvement with low rates of intracranial hemorrhage [14,15]. The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA Stroke Study Group trial [3] was the first landmark trial to demonstrate the effectiveness of fibrinolytic therapy for AIS and helped to establish IV-tPA as a standard of care. The NINDS trial was a double-blinded, randomized, placebo-controlled trial, and enrolled patients with AIS within 3 h from symptom onset. All patients had to have a clearly defined time of onset of their ischemic symptoms, a measurable neurological deficit using the National Institute of Health Stroke Scale (NIHSS), and no evidence of intracranial hemorrhage (ICH) on their admission cranial computed tomography (CT) scan (Fig. 1). The exclusion criteria included a past history of ICH or an ischemic stroke within 3 months, symptoms suggestive of subarachnoid hemorrhage, any major surgery within 14 days, recent history of gastrointestinal hemorrhage or urinary tract hemorrhage in the past

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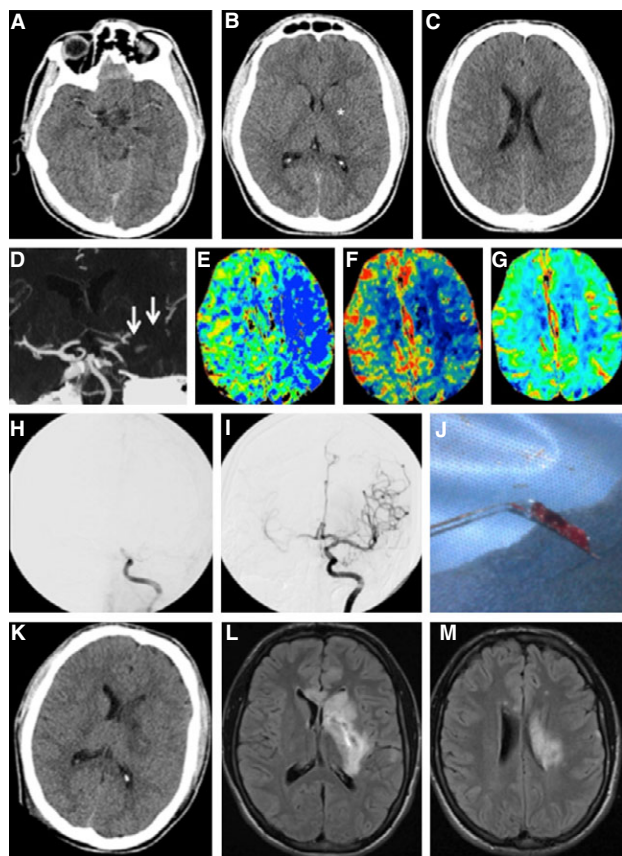E-mail: vanadel@hhsc.ca

Fig. 1. This patient presented with global aphasia and right hemiparesis (NIHSS =18). (A–D) Left MCA proximal occlusion ischemic stroke with a hyperdense left MCA on the admission non-contrast CT (NCCT) scan and early ischemic changes * within the lentiform nuclei and CT angiography confirmed a left MCA proximal vessel occlusion. (E–G) CT perfusion imaging (E, mean transit time [MTT], F, cerebral blood flow [CBF], G, cerebral blood volume [CBV] demonstrates a small core ischemic infarction within the lentiform nuclei and a large area of penumbra within the left hemisphere. (H–J) Digital substraction angiographic views (anteroposterior, AP), H shows a carotid T occlusion and complete angiographic reperfusion (I) after mechanical thrombectomy using a TrevoStentretreiver (J). (K–M) Follow up NCCT and MRI imaging demonstrates a subcortical infarct similar to the admission NCCT in B. The patient's 90 day mRS is 2.

3 weeks or arterial puncture at a non-compressible site within the last week, uncontrolled hypertension (> 185/110) or aggressive treatment to lower the blood pressure < 185/110. Patients were also excluded whether they were taking any anticoagulant or received heparin within 48 h prior to the onset of their AIS. Patients were not eligible for enrollment in the trial if their admission laboratory investigations showed an elevated partial-thromboplastin time; prothrombin times > 15 s; platelet count of less than 100 000/mm^3, or a serum glucose below 2.7 mmol L^{-1} or > 22.2 mmol L^{-1}. Recombinant t-PA was used in the active treatment arm at a dose of 0.9 mg kg^{-1} with a maximum dosage of 90 mg. A bolus dose of 10% of the total dose was administered over the

first minute, while the remaining 90% was administered over the next hour. The control group received a placebo IV treatment. The first part of the trial (291 patients) looked at neurological improvement at 24 h as a primary outcome and was unable to demonstrate a significant difference between the two groups. It was noticed that the 3 months rate of excellent functional outcome, a secondary outcome, was significantly better in the t-PA group (mRS 0–1 achieved in 47% vs. 27% in the placebo group, $P < 0.001$). A second part for this trial was attempted (333 patients), using excellent functional outcome at 3 months as the primary outcome. An excellent functional outcome (no or minimal residual symptoms) was defined as modified Rankin score (mRS) of 0 or 1, NIHSS ≤ 1, Glasgow outcome scale of 1, or Barthel index of 95–100 at 3 months clinical follow-up. For the 333 patients randomized in this second part, the mean delay for treatment was 120 min, with half of the cohort enrolled within the first 90 min after symptoms onset. The clinical severity of the stroke was similar in both groups (NIHSS of 14). In the t-PA group, 39% observed a mRS score of 0 or 1 as compared to 26% in the placebo group ($P = 0.019$). Combined, the two parts of this trial showed a higher likelihood of long-term excellent functional outcome in the t-PA group (patients treated within 90 min: OR 1.9 [1.2–2.9], patients treated between 90 and 180 min: OR 1.9 [1.3–2.9]). The rate of symptomatic intracranial hemorrhage (sICH) was significantly higher in the t-PA group (6% vs. 0.6%, $P < 0,001$), but the mortality rate was still slightly lower when compared to placebo (17% vs. 21%, $P = 0.30$).

Unfortunately, only a fraction of patients with AIS would present and be treated within the narrow time window of three hours from symptom onset. Several trials, including the first and second European Cooperative Acute Stroke Study (ECASS) trials that enrolled over 1400 patients, attempted to demonstrate effectiveness of tPA up to 6 h after symptom onset [11,12]. However, these studies were unable to demonstrate a benefit of IV tPA beyond a 3-h window. A few years later, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS B) trial, enrolling 613 patients treated from 3 to 5 h with IV-tPA was stopped due to futility [13]. Several years later, ECASS III trial was designed to assess safety and efficacy of IV t-PA up to 4.5 h after symptoms onset [16]. The primary outcome was the proportion of patients with no or minimal residual symptoms at 3 months (mRS 0–1). A total of 821 patients were randomized to receive t-PA or placebo in a protocol similar to the NINDS trial. The mean time to treatment from symptom onset was 240 min, and the median NIHSS was 10 (similar in both groups). More patients in the IV-tPA group experienced an excellent functional outcome at 3 months compared to the control group (52.4% vs. 45.2%; $P = 0.04$). The rate of sICH was again ten times higher in the t-PA group (2.4% vs. 0.2%, $P = 0.008$) but

without significant impact on mortality when compared to placebo group (7.7% vs. 8.4%, *P* = 0.68).

The publication of ECASS III in 2008 allowed the expansion of the clinical window for IV-tPA from 3 to 4.5 h. However, ECASS III excluded patients over 80 years of age, those with severe strokes (clinically with NIHSS > 25, or radiologically with more than one-third of middle cerebral artery territory involved) and patients with a combination of diabetes and prior stroke.

In the third International Stroke Trial (IST III) [17], the investigators sought to determine whether t-PA could be administered to a wider range of patients (especially those over 80 years of age, who were excluded from most previous trials) with an extended time window of six hours from onset. The primary outcome was the proportion of patients with functional independence at 6 months follow-up (Oxford Handicap Score [OHS] 0–2). The trial enrolled 3035 patients randomly assigned to receive either intravenous t-PA or placebo. The mean age of the patients was 77, with more than half of the cohort being older than 80 years of age and 42% of the subjects treated between 4.5 and 6 h from symptoms onset (mean time to treatment 252 min). The study showed no significant benefit of intravenous t-PA compared with placebo for the primary endpoint, but at 6 months, a higher proportion of patients in the t-PA group had no or minimal residual symptoms (OHS 0–1 in 24% vs. 21%, *P* = 0.018). The benefit of t-PA was greater in those treated within 3 h of symptom onset, but was also surprisingly more favorable in patients more than 80 years of age (*P* = 0.029 for treatment-by-age interaction). Interestingly, there was no additional harm with IV t-PA despite the extended time window and the inclusion of older patients (sICH rate of 7% compared to 1% in the control group; mortality rate at 6 months of 27% in both groups).

To date, IV thrombolysis with tPA is the only established lytic agent with evidence for use in patients with AIS. A recent meta-analysis gathering data from all major trials on t-PA for acute ischemic stroke confirms that t-PA increases the likelihood of favorable long-term functional outcome when given within 4.5 h (Table 1) [18]. This effect is irrespective of stroke severity and is significantly stronger when treatment is administered earlier and patients over 80 years of age appear to have an even greater benefit. While initial stroke severity and age are important prognostic factors, the time from onset of symptoms to administration of t-PA remains the main determinant of the effectiveness of the therapy [19]. Indeed, the concept of 'time is brain' implies the urgency and ability of having well-established systems and comprehensive stroke centres in place to rapidly assess patients and initiate treatment with IV thrombolysis, as every minute in delaying treatment leads to a reduction in the likelihood of a good functional outcome [20]. Moreover, for large proximal vessel occlusion ischemic strokes, it has been estimated that on average, 1.9 million neuron die with every minute of ischemia [21], underscoring the crucial impact of treatment delay.

Clot composition and recanalization

Several lines of evidence suggest that the radiological appearance of an occluded intracranial vessel might be correlated to the etiology of the stroke as well as the composition of the clot, and therefore, may help predict the likelihood of recanalization with IV thrombolysis and/or endovascular therapy [22,23]. Studies looking at the composition of clots extracted from intracranial arteries in acute ischemic stroke setting by mechanical devices have shown two main types of clot compositions [24]. 'Red clots' are composed mainly of red blood cells, fibrin, and with high hematocrit levels, are routinely classified as being hyperdense clots (measured with Hounsfield unit, HU values) on a non-contrast cranial CT scan (Fig. 1, example of a 'Hyperdense MCA sign'). 'White clots' are mainly composed of platelets, atheromatous, and cellular debris and tend to show a lower density (measured HU values) on non-contrast cranial CT images. Low clot density and longer thrombus length are clot characteristics that are more resistant to fibrinolysis and mechanical extraction.

Table 1 Main results of major trials on IV t-PA in AIS

Trial	Number of patients	Time window from symptom onset	Mean age	Median NIHSS	Mean treatment delay (minutes)	Rates of favorable outcome (OHS or mRS 0–1) compared to placebo	*P*-value
NINDS part 1	291	0–3 h	67	14	120	47% vs. 27%	< 0.001
NINDS part 2	333	0–3 h	68	14	120	39% vs. 26%	0.019
ECASS I	620	0–6 h	65	12	264	35.7% vs. 29.3%	0.41
ECASS II	800	0–6 h	66	12	258	40.3% vs. 36.6%	0.277
ECASS III	821	3–4.5 h	65	10	240	52.4% vs. 45.2%	0.04
ATLANTIS B	549	3–5 h	66	11	258	34% vs. 32%	0.65
IST-3	3035	0–6 h included patients > 80 years of age	77	12	252	24% vs. 21%	0.018

In AIS, the chances of a favorable outcome are closely related to the recanalization of the occluded vessel [2]. Clot characteristics other than clot density are best assessed by CT angiogram and have also been correlated to the likelihood of successful recanalization and a favorable outcome. It has been shown that a clot of 8 mm or greater in length consistently have poor rates of successful recanalization (≤ 1%) with IV t-PA alone [25]. Moreover, the site of the occlusion may help predict the chances of successful recanalization with thrombolytic therapy: 44% in distal middle cerebral artery, only 30% in proximal middle cerebral artery and as low as 6% in terminal internal carotid artery and 4% in the basilar artery [26].

Other thrombolytic agents and heparinoids have been tested in AIS but most have failed to demonstrate a clinical benefit or were not retained for clinical use. Recent data suggest that TNK-tPA (tenecteplase) could benefit patients presenting with acute minor strokes (NIHSS < 6) and intracranial vessel occlusion [27]. In addition, there is some promise in techniques aimed to augment the fibrinolytic effects of IV-tPA, such as the use of ultrasound-enhanced thrombolysis. The efficacy of clot lysis with intravenous t-PA maybe enhanced with the use of transcranial ultrasounds [28]. This technique is especially interesting considering its ease of administration (headframe installation without any needed skills in ultrasounds) and hence the potential to render it widely available. A large randomized trial is currently ongoing to verify the potential benefits or harm of this approach (ClinicalTrials.gov: CLOTBUST-ER NCT01098981).

Intra-arterial therapy

Clinical outcomes for patients with large proximal occlusions are poor with up to 80% not regaining functional independence after stroke even if they receive IV thrombolysis [8,29]. For the past decade, alternative approaches to recanalize occluded intracranial vessels more effectively have been studied. This has lead to the progressive development of endovascular therapies that initially showed very promising results with improved rates of recanalization and functional outcomes [4,30]. However, in 2013, three prospective randomized control trials (Interventional Management of Stroke, IMS-III; the Mechanical Retrieval and Recanalization of Stroke Clots using Embolectomy, MR RESCUE; and the SYNTHESIS-Expansion trial) failed to demonstrate any added benefit of the endovascular therapies over the traditional intravenous thrombolysis or standard of care treatment for AIS [29,31,32]. The lack of success of these three trials was largely attributed to the use of older devices prolonging times to recanalization and enrollment of patients without intracranial large vessel occlusion (LVO) in the intra-arterial therapy (IAT) arm. Device technologies have rapidly evolved for both mechanical thrombectomy and mechanoaspiration techniques [33], allowing neurointervention-
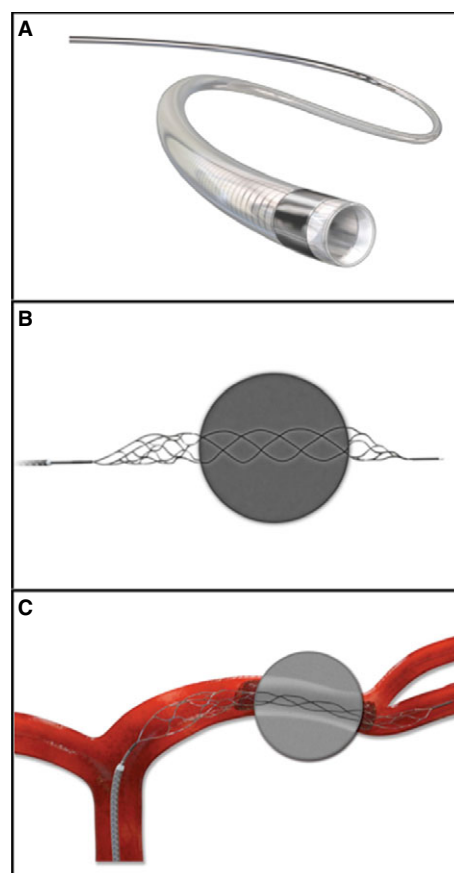

Fig. 2. Representative images of the newer devices used for intra-arterial mechanical thrombectomy large vessel acute ischemic stroke. (A) Penumbra (ACE, clot extraction device) aspiration catheter (courtesy of Penumbra, Inc.); (B,C) Trevo Pro Vue stentretriever catheter (courtesy of Stryker Neurovascular By Concentric Medical.) A self expandable stent is deployed and opened within the clot to engage it within the mesh of the stent. The stent is subsequently retrieved by removing the stent under flow arrest.

ists to drastically reduce procedural times, with improved rates of recanalization and better clinical outcomes (Fig. 2). Several recent trials have demonstrated superiority of these newer devices with impressive rates of recanalization (up to 68%)and reduced time to recanalization when compared to first-generation tools [5,6]. The retrievable stents, or stentrievers, and large bore aspiration catheters are now the most widely used tools for endovascular recanalization in AIS [7,34].

Within the past few months, several recently published landmark trials (1: Multicenter Randomized Clinical Trial of Endovascular treatment for AIS in the Netherlands [MR-CLEAN]; 2: Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE]; 3: Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial [EXTEND-IA]) have now established the safety and efficacy of IAT in patients with LVO of the anterior cerebral circulation (Table 2). The MR CLEAN trial was the first of several positive

Table 2 Summary of the most recent trials on endovascular treatment for AIS.

Trial	Number of Patients	Mean Age	Median NIHSS	Mean onset of symptoms to groin puncture time (minutes)	Favorable recanalization (TICI 2B-3)*, %	Favorable outcome mRS 0–2†	sICH†	Death†
MR CLEAN	500	65	17	260	58.7	32.6% vs. 19.1%	7.7% vs. 6.4%	21% vs. 22%
ESCAPE	316	71	16	N/A	72.4	51.6% vs. 23.1%	3.6% vs. 2.7%	10% vs. 19%
EXTEND-IA	70	70	17	210	86	71% vs. 40%	0% vs. 6%	9% vs. 20%

*Thrombolysis In Cerebral Infarction score at the end of the endovascular procedure. †Rates of endovascular treatment arms compared to standard treatment groups.

multicentre randomized control trials to be published demonstrating the superiority of IAT over standard medical treatment in AIS [8]. The trial enrolled patients with LVO and had no upper age limit and patients could be randomized up to 6 h after symptoms onset. A proximal LVO (distal internal carotid artery, M1 or M2 segment of middle cerebral artery, A1 or A2 segment of anterior cerebral artery) was demonstrated by either computed tomography (CT) angiography, magnetic resonance angiography, or digital subtraction angiography prior to enrollment. In this trial, 500 patients were randomly assigned to receive endovascular intervention plus usual care (including IV t-PA) or usual care alone in the setting of AIS. The vast majority of patients (89%) received intravenous t-PA (mean treatment delay of 86 min). For patients randomized to receive endovascular intervention, the IAT was instituted within 260 min on average, and the most were treated with retrievable stents (81.5%). Three months after the initial stroke, there was an absolute difference of 13.5% (95% CI [5.9–21.2]) in the rate of functional independence (mRS 0–2) in the intervention group (32.6% vs. 19.1%). There were no major clinically meaningful adverse events resulting from the endovascular technique (rate of serious adverse events 47.2% vs. 42.3%, $P = 0.31$). The rate of sICH was similar in both groups (7.7% vs. 6.4%). The use of IAT resulted in recanalization rate of 58.7% (Thrombolysis In Cerebral Ischemia [TICI] score of 2B-3) by the end of the procedure. The endovascular treatment group also achieved significantly lower final infarct volume (49 mL vs. 79 mL). With the MR CLEAN trial clearly demonstrating the superiority of IAT, this promoted the early cessation of other trials (ESCAPE and EXTEND-IA) aiming to prove the benefits of IAT.

The ESCAPE trial [9] was an open-label trial with blinded outcome assessment randomizing AIS patients within 12 h from onset of symptoms. Participants had to have a small infarct core, a proximal intracranial vessel occlusion and a favorable pattern of collateral flow as demonstrated by multiphase CT angiogram prior to enrollment. Patients were treated with IAT plus standard care or standard care alone. The trial was stopped early for efficacy after 316 patients were enrolled (120 in the endovascular arm, 118 in the standard treatment arm). These patients had significant clinical deficits with median

NIHSS of 16. Stentrievers were used in 86% of patients in the IAT arm, achieving first reperfusion at a median of 241 min after symptoms onset. The endovascular group benefited from IV tPA administration in 73% of cases, whereas 79% of the standard care group received IV tPA. After 3 months, patients in the endovascular group achieved a favorable functional outcome (mRS 0–2) in 51.6% of cases compared to 23,1% in the standard treatment group (absolute difference 23.8%; 95% CI [13.2–34.4]). There was no difference in the rates of sICH (3.6% vs. 2.7%), but the mortality rate at 3 months was lower in the endovascular group (10.4% vs. 19%, absolute difference 8.6%, 95% CI [0.8–16.6]).

EXTEND-IA [10] is the third randomized trial demonstrating superiority of adding mechanical thrombectomy to standard care over standard care alone in patients with proximal LVO. In this study, patients were randomized within 4.5 h from symptom onset and had to be eligible to receive IV t-PA as the standard treatment. For IAT, stentrievers were used as the primary reperfusion tool. Patients were excluded if they presented an ischemic core volume of more than 70 mL as demonstrated by CT perfusion imaging prior to enrollment. Enrollment was stopped early after 70 patients (35 in each arm) for efficacy of intervention. Endovascular treatment was initiated on average within 210 min after symptoms onset. High rates of recanalization (86% with favorable reperfusion score TICI 2B-3) were obtained by the end of the endovascular procedure. At 3 months, a favorable functional outcome (mRS 0–2) was achieved in 71% of patients treated with IAT compared to only 40% in the standard treatment group ($P = 0.009$). None of the patients in the stentriever group experienced a sICH whereas it affected 6% of the standard treatment group. Similar to the ESCAPE trial, there was a clear benefit for patients in the IAT group, with a significant reduction in mortality at 3 months (9% vs. 20%).

The results of MR CLEAN, ESCAPE, and EXTEND-IA are overwhelmingly in favor of adding endovascular therapy to standard care including IV-tPA in patients presenting within 6 h with a proximal LVO ischemic stroke. However, very few patients were randomized beyond 6 h and no clear conclusion can be drawn for this specific subgroup of patients. A recently published meta-analysis

of prospective randomized controlled trials comparing endovascular therapies with standard of care/medical management in patients AIS clearly demonstrates superior outcomes in patients treated with IAT [35]. The major difference between these three trials relied in their imaging-based inclusion criteria. ESCAPE and EXTEND-IA used advanced vascular imaging beyond simple CT angiogram (multiphase CTA and CT perfusion, respectively) to try to better identify favorable ischemic penumbra (potentially salvageable brain tissue vs. irreversibly injured/infarcted tissue). It is yet to be determined whether such imaging-based criteria confers an increased likelihood of a better clinical outcome. The small number of patients enrolled in ESCAPE and EXTEND-IA and the fact that the trials were stopped prematurely may potentially lead to overestimation of benefit from pre-selection of patients based on imaging the ischemic penumbra and collateral blood flow. We see from the results of MR CLEAN, that even without this 'pre-selection' of patients for revascularization, clot retrieval remains extremely effective.

Conclusion

The mainstay of treatment for acute ischemic stroke remains intravenous t-PA, with best outcomes achieved when treatment is administered early after symptoms onset. Owing to the recent publication of three positive trials, the endovascular approach for acute ischemic stroke treatment has become a game changer in the paradigm of stroke therapeutics and will likely become a new standard of care in the near future. However, this new approach still requires highly specialized stroke centres and for now will continue to be available for only a small percentage of patients. It is yet to be determined how this technique could be generalized and integrated in the current stroke care organization, considering its expensive cost and low availability in most countries.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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