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Cerebrovascular Disease and Stroke (D Greer, Section Editor)

Intra-Arterial Treatment of Acute Ischemic Stroke: The Continued Evolution

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Opinion statement

The devastation caused by acute ischemic strokes is evident in every intensive care unit across the world. Although there is no doubt that progress has been made in treatment, it has been slow to come. With the emergence of new tech-

nologies in imaging, thrombolysis and endovascular intervention, the treatment modalities of acute ischemic stroke will enter a new era. In this review, we present the concept of the seven evolutionary phases in the treatment of acute ischemic stroke to date.

Introduction

Phase I: "To know your future, you must know your past, each stepping stone that has been cast" – Margaret Jang

The first description of stroke dates back to 400 B.C. when Hippocrates established the foundations of modern medicine. From his observations of patients with brain injury, he described concurrent episodes of convulsions, speech impairment and paralysis. Because the onset would be sudden and intense, Hippocrates named these symptoms "apoplexy," meaning "struck with violence" in Greek [1]. The next millennium yielded few insights regarding stroke. Throughout the Medieval and Renaissance Periods, physicians believed that an overabundance of blood caused stroke; bloodletting became the gold standard for treating mild cases of stroke [2].

The word "stroke" first appeared in the English literature in 1599 and was used mostly by laypersons [3]. A major advance in stroke literature came in 1665 when the English physician Thomas Willis described the cerebral arteries, specifically the Circle of Willis, in his text *Cerebri Anatome*. He hypothesized that redundancies in blood supply to the same region of the brain could prevent stroke. By the nineteenth century, German pathologist R.L.K. Virchow postulated that ruptured blood vessels and thromboembolism caused stroke [4]. The theory for injury was that cerebral blood flow could be obstructed due to thrombosis. To describe the downstream loss of perfusion, Virchow coined the term "ischemia" [5].

In the early twentieth century, physicians emphasized the connection between the pathophysiology of stroke and its visible clinical signs. The French neurologist Charles Foix pioneered the field of vascular neurology when he traced the deep and superficial branches of cerebral arteries, which he correlated with the brain's nuclear structures and accompanying clinical neurological signs [5]. C. Miller Fisher, a Canadian neurologist, expanded this field by describing the pathology of lacunar infarcts, carotid artery occlusions and brain hemorrhages [5]. His work elucidated the thromboembolic mechanism that underlies ischemic stroke and postulated that thrombi originate from either the heart or proximal arterial lesions [6].

Our understanding of stroke pathophysiology and its management has since grown exponentially with the advent of imaging technologies, pharmacological agents, intra-arterial (IA) interventions and stroke units.

Phase II: "True progress quietly and persistently moves along without notice." – Saint Francis de Sales

Stroke is the fourth leading cause of death in the United States with 795,000, new or recurrent events annually, accounting for one in every 19 deaths [7]. Ischemia accounts for 87 % of strokes; 80 % of these cases show evidence of arterial occlusion on cerebral angiography [8].

The only FDA-approved treatment for stroke is intravenous tissue plasminogen activator (IV t-PA). In the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial, investigators compared IV t-PA and placebo administered within 3 h of stroke onset [9]. With CT imaging to exclude patients with hemorrhagic stroke, patients provided IV t-PA obtained significantly greater independent and functional clinical outcomes compared to placebo at 90 days post-stroke (modified Rankin Scale 0–1: 39 % vs. 26 %). The European Cooperative Acute Stroke Study (ECASS) III study of 821 patients demonstrated that recombinant IV t-PA, alteplase, can be effective also up to 4.5 h after stroke onset [10]. The study results mirrored that of the NINDS study, with better clinical outcomes at a cost of a higher risk of intracerebral hemorrhage. However, ECASS III showed no statistical difference in patient mortality at 90 days.

Major therapeutic advancements, such as IV thrombolysis, have decreased the number of deaths from stroke by 23 % between 1999 and 2009 [7]. However, the majority of patients do not qualify for IV thrombolysis, and many who survive live with severe disabil-

ities [11]. Fewer than 10 % of patients meet the eligibility criteria for IV t-PA because the standard treatment window is 4.5 h or less [9, 12]. Furthermore, as many as 20 % patients who improve initially with intravenous thrombolysis experience clinical deterioration, possibly due to vessel re-occlusion [13].

To date, PROACT II (Prolyse in Acute Cerebral Thromboembolism II) is the only randomized trial on the safety and efficacy of intra-arterial chemical thrombolysis in ischemic stroke [14]. In 180 patients with angiographically identified middle cerebral artery occlusions, the investigators found that patients given intra-arterial recombinant pro-urokinase (r-pro-UK) and IV heparin within 6 h of stroke onset achieved higher recanalization rates compared to the control group of IV heparin only (66 % vs. 18 %), correlating with a higher proportion of good neurological outcomes (modified Rankin Scale 0–2: 40 % vs. 25 %). Despite these positive results, the FDA decided against approval of intra-arterial thrombolysis with r-proUK. They cited the study's insufficient statistical power and higher rates of intracranial hemorrhage with neurological deterioration defined as a 4-point or more increase to the total National Institute of Health Stroke Scale (NIHSS) score or a 1-point increase in the level of consciousness on the NIHSS within 24 h (10 % vs. 2 %) [14]. However, this therapy continues to be used off-label in patients refractory or ineligible for IV t-PA.

In addition to intra-arterial thrombolysis, another endovascular option for treating acute ischemic stroke is mechanical recanalization, which focuses on recanalization of occluded proximal vessels to reperfuse and salvage downstream ischemic tissue. For example, Figure 1 shows cross recanalization by delivery of t-PA into the contralateral middle cerebral artery via the anterior communicating artery. In a meta-analysis of 53 case series, case–control and randomized-control studies from 1985 to 2002 of spontaneous or therapeutic recanalization in acute ischemic stroke [15], vessel recanalization was associated with a 4 – 5-fold increase in good functional outcomes and decrease in mortality. Studies have shown that IV thrombolysis is insufficient and only achieves 10 – 30 % recanalization of large vessel occlusions [16].

Phase III: "Technology is a queer thing… It brings you great gifts with one hand and stabs you in the back with another" – Carrie Snow

After an ischemic insult, cell death will spread slowly from a core of severely and rapidly injured brain tissue (irreversible infarct) to a heterogeneous region called the penumbra (reversible ischemia) [17]. With early endovascular recanalization using either intra-arterial thrombolysis (IA t-PA) or mechanical thrombectomy, the final infarct volume may be limited by potentially salvaging the compromised penumbral tissue.

Clot retrieval theoretically could be more effective than IV or IA t-PA on thromboemboli resistant to enzymatic fibrin degradation, such as a mature thrombus containing cross-linked fibrin, calcium, cholesterol crystals, or platelet-rich components [18]. Mechanical thrombectomy has been demonstrated to be safe within 8 h of stroke onset. The FDA approved the first generation of thrombectomy devices in 2004 with the Merci Retriever system. The Merci Retriever has since undergone three different designs, with the latest generation possessing a non-tapered filamented helical coil. In the pilot MERCI I (Mechanical Thrombectomy for Acute Ischemic Stroke) trial of 30 patients in seven US centers, this device alone resulted in recanalization in 43 % of stroke patients with NIHSS scores greater than 10 [19]. The recanalization rate increased to 64 % when the Merci Retriever was used in combination with IV t-PA. The phase 2 MERCI and Multi-MERCI trials compared mechanical recanalization in 141 and 164 patients, respectively [20, 21]. Both studies were prospective and multicenter single arm trials that treated patients up to 8 h after stroke onset with major cerebrovascular occlusions and NIHSS scores greater than 8. In the MERCI trial, 48 % of patients were recanalized using the Merci Retriever and 60.3 % were recanalized when adding adjunctive IV t-PA. With successful recanalization, 30-day mortality decreased (23.9 % vs. 49.3 %) and 30-day NIHSS scores significantly improved (54 % vs. 16 %). The Multi-MERCI trial yielded similar results with 55 % recanalization using device alone and 68 % with adjunctive IV t-PA therapy. Good clinical outcomes (mRS 0–2) were observed in 36 % of patients, but no control groups were available for comparison.

The Penumbra System, the second generation of thrombectomy devices, received approval in the United States in 2008 under a 510(k) clearance from the FDA. It consists of a reperfusion catheter attached to a suction pump and microwire, which allows for thrombus debulking and aspiration for site-directed thrombus extraction. In the prospective, multicenter and single-arm study of 125 patients, the Penumbra Pivotal Stroke Trial found that the Penumbra System yielded a recanalization rate of 81.6 % with a Thrombolysis in Myocardial Infarction (TIMI) score of II or

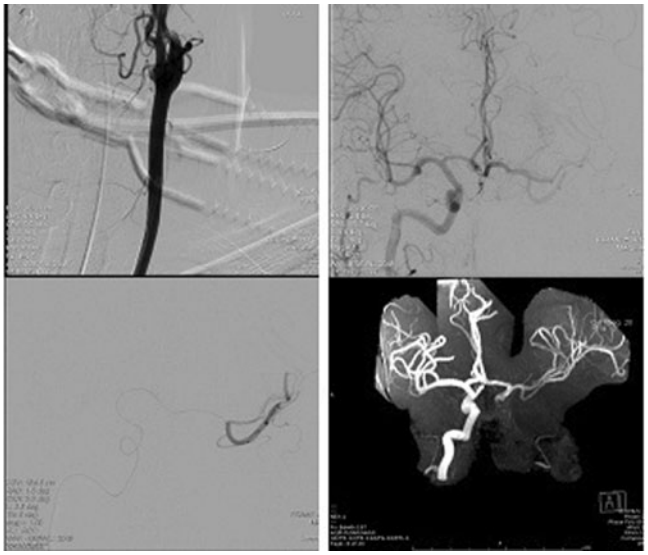

Figure 1. Cross recanalization by delivery of t-PA into the contralateral middle cerebral artery via anterior communicating artery (Images courtesy of K. Bulsara, J. Aruny and J. Schindler.)

better [22]. However, only 25 % of patients achieved good clinical outcomes at 30 days (4-point or greater improvement NIHSS score and/or a mRS 0–2). In the subsequent Penumbra POST trial, a retrospective case review of 157 consecutive patients, 87 % recanalization using the Penumbra System correlated with 45 % of patients being independent (mRS 0–2) at 30 days [23].

A third generation of mechanical thrombectomy devices includes the stent retrievers and stent thrombectomy hybrids. Both the Trevo Retriever (Stryker Corporation) and Solitaire Flow Restoration (Covidien) devices received FDA approval in 2012. Stent retrievers are hybrid devices that combine features of intracranial stents and clot retrievable devices. Both the Trevo and Solitaire stent retrievers have demonstrated superiority compared to previous generation devices. In the TREVO 2 randomized trial of 178 patients, the Trevo device outperformed the Merci Retriever with both higher recanalization rates (86 % vs. 60 %) and better clinical outcomes (90 day mRS 0–2; 40 % vs. 22 %) [24]. In the SWIFT trial of 113 patients comparing the Solitaire flow restoration device and the Merci Retriever, the Solitaire device also demonstrated higher recanalization rates (61 % vs. 24 %) [25], improved 90-day neurological outcomes (mRS 0–2; 36 % vs. 29 %), and lower 90-day mortality rates (17 % vs. 38 %).

The literature suggests that endovascular IA therapy recanalizes large artery occlusions more frequently and rapidly than IV t-PA alone in patients with acute ischemic stroke. Endovascular therapy is increasingly used when patients are ineligible for IV t-PA or when it is ineffective, particularly in large vessel and/or long segment cerebrovascular occlusions [26].

Phase IV: "A critic is someone who enters the battlefield after the war is over and shoots the wounded." – Murray Kempton

Despite advancements in endovascular techniques, there is a disparity between recanalization and clinical outcomes. Death still occurs in 26 – 36 % of patients despite recanalization [27]. Recanalization of large vessel occlusions may be ineffective because of distal small vessel emboli, and may occur too late to salvage ischemic tissue. Recanalization may also exacerbate tissue injury by promoting reperfusion injury, excessive cerebral edema and hemorrhagic transformation [15]. Clinical outcomes may be influenced by various other factors, many of which are related to patient selection. These factors include age, gender, severity of deficits on presentation, collateral blood flow, ratio of salvageable ischemic tissue to completed infarct volume, baseline co-morbidities such as diabetes mellitus and hypertension, and post-stroke management, rehabilitation, and secondary prevention.

The Agency for Healthcare Quality and Research concluded that this area lacks high-quality research and many unanswered questions remain regarding op-

timal thrombectomy devices, their efficacy and safety [28]. Currently, there are 12 ongoing randomized, controlled and three prospective cohort studies with projected enrollments between 20 and 2,000 participants that will investigate at least one neurothrombectomy device in acute ischemic stroke (Table 1).

The approval process for new neurothrombectomy devices, regulated by the FDA Center for Device and Radiological Health, also received criticism from organizations such as the Institute of Medicine. These devices go through the 510(k) premarket notification process and must only demonstrate that a new device is equal in safety and effectiveness to existing devices.

There is a call to reassess endovascular intervention as we move out of the infancy of neurointerventional therapy. Our first need is for better clinical trial data. Between 1995 and 2012, 13 prospective randomized trials showed an increase in mean time from symptom onset to endovascular treatment with severe delays due to stroke system processes. Although a significant increase in recanalization rates was noted in more recent clinical trials [29], these improvements did not translate into better clinical outcomes or mortality since the NINDS trial of 1995.

Table 1. Ongoing studies of neurothrombectomy devices investigating ischemic stroke

ClinicalTrial.gov Identifier	Study Name	Anticipated Completion Date	Design	Projected Enrollment
NCT00785161	PICS: Penumbra Imaging Collaborative Study	Nov. 2013	PCS	2,000
NCT01455935	WASSABI: Wake up Symptomatic Stroke- Benefit of Intravenous Clot Busters or Endovascular Intervention	Dec. 2013	RCT	90
NCT00359424	IMSIII: Interventional Management of Stroke III Trial	Jun. 2014	RCT	900
NCT01895634	RIVER JAPAN: Reperfuse Ischemic Vessels With Endovascular Recanalization Device in Japan	Jun. 2014	RCT	50
NCT01584609	A Randomized, Concurrent Controlled Trial to Assess the Safety and Effectiveness of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke	Jul. 2014	RCT	230
NCT01560247	PRIISM2: Percutaneous Recanalization in Ischemic Stroke Management in Europe Observational Registry	Sep. 2014	PCS	100
NCT01778335	ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke	Dec. 2014	RCT	250
NCT01492725	EXTENDA-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial	Dec. 2014	RCT	100
NCT01869478	EARLY: Feasibility Study of IV rtPA vs. Primary Endovascular Therapy for Acute Ischemic Stroke	Feb. 2015	RCT	20
NCT01692379	REVASCAT: Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours	Oct. 2015	RCT	690
NCT01852201	POSITIVE: Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy	Jun. 2016	RCT	750
NCT01429350	THERAPY: Assess the Penumbra System in the Treatment of Acute Stroke	Oct. 2016	RCT	692
NCT01745692	PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation	May 2017	RCT	800
NCT01657461	SWIFT PRIME: Solitaire™ FR as Primary Treatment for Acute Ischemic Stroke	Jun. 2018	RCT	833
*	TREVO: Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke Registry	*	PCS	*

RCT=randomized control trial; PCS=prospective control study; *New registry to be initiated

Phase V: "The beginning of knowledge is the discovery of something we do not understand." – Frank Herbert

Several recently published studies have advanced our understanding of endovascular treatment for stroke. The Interventional Management of Stroke Trial III (IMS III) compared IV thrombolysis combined with endovascular therapy using FDA-approved devices versus IV thrombolysis alone [30•]. In this randomized, open-label multicenter trial, subjects received treatment within 3 h of symptom onset, and the study was projected to enroll 900 subjects with moderate to severe ischemic stroke starting in August 2006. The trial was stopped at 656 participants in April of 2012 after a futility analysis demonstrating no functional benefit to endovascular therapy. Subjects in both groups showed similar functional outcomes (mRS 0–2: 40.8 % intervention vs. 38.7 % IV tPA control) and risk of symptomatic intracranial hemorrhage (6.2 % vs. 5.9 %). However, a subgroup analysis of IMS III suggested that patients with large vessel occlusions had significantly better recanalization rates with endovascular treatment compared to IV t-PA alone (81 % vs. 40 % in M1 occlusions). Additionally, patients with severe presentations (NIHSS>20) and those receiving IV t-PA in under 2 h trended toward a statistical benefit in clinical outcomes.

The Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) trial compared intra-arterial thrombolysis and/or endovascular treatment and systemic IV thrombolysis for acute ischemic stroke in a multicenter, randomized trial [31•]. Three hundred and sixty-two patients received either IV t-PA within 4.5 h of stroke onset or intra-arterial t-PA/thrombectomy within 6 h of stroke onset. Ninety-day morality did not differ. Although the results did not indicate a clinical or mortality benefit for intra-arterial therapy, the study was heavily criticized for delaying treatment to patients in the endovascular arm and for not excluding patients with no documented large vessel occlusion.

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) multicenter randomized controlled trial compared standard medical care to embolectomy (Merci Retriever or Penumbra System) in patients presenting within 8 h with large vessel anterior circulation strokes [32•]. They characterized patients as having a favorable penumbral (infarct core <90 mL and perfusion/core mismatch ratio of 1.4) or non-penumbral pattern using both CT/MR perfusion imaging, but patients were randomized equally regardless of imaging findings. Embolectomy was found not to be superior to medical therapy in patients with either favorable or unfavorable penumbral patterns, but the study was mired by slow recruitment for 8 years, markedly delayed randomization and groin puncture times (> 5 – 6 h), and unsubstantiated CT/MR perfusion imaging metrics to define ischemia versus oligemia.

In contrast, the DEFUSE II trial was a prospective cohort study that evaluated whether MRI-based patient selection could improve clinical outcomes following endovascular therapy [33•]. Target mismatch was more stringently defined than in the MR RESCUE and previous DEFUSE studies to ensure a large volume of salvageable ischemic tissue based on the difference in perfusion and diffusion-weighted imaging (PWI/DWI mismatch ratio >1.8). In a cohort of 123 subjects with endovascular thrombectomy within 12 h of stroke onset, target mismatch patients who had early reperfusion demonstrated markedly favorable clinical responses (OR 8.8) and good 90-day functional outcomes (mRS 0–2) (OR 4.0, 56 % vs. 31 %).

Although conclusions drawn by recent clinical trials have been inconsistent, these studies do indicate that not all patients benefit from interventional therapy. These trial designs and results, however, have many shortcomings. For instance, the IMS III, SYNTHESIS and MR RESCUE trials primarily used older generation thrombectomy devices rather than the newest generation of stent retrievers. As a result, recanalization rates and effective reperfusion (Thrombolysis in Cerebral Infarction or TICI>2b) in these studies are among the lowest ever reported [34]. IMS III had a recanalization rate of 40 %. SYNTHESIS only used thrombectomy devices in one-third of their endovascular intervention group; this trial also failed to report recanalization rates and the presence of large vessel occlusions. The MR RESCUE recanalization rate of 27 % is lower than any trial using newer thrombectomy devices.

The time between stroke onset and interventional therapy also varied among studies. In the SYNTHESIS trial, intra-arterial therapy took an average of 1 h longer to initiate than IV t-PA only (3.75 vs. 2.75 h). MR RESCUE had an average stroke onset to groin puncture time of 6.3 h for intra-arterial therapy. Furthermore, the penumbral classification in MR RESCUE posed several limitations. The algorithm failed to classify 42 % of cases (excluding those patients from the study), and the ones that were selected had a signifi-

cantly larger infarct cores compared with other imaging trials. Both CT and MR perfusion modalities were mixed, with less stringent patient selection than in DEFUSE-2 (perfusion/core mismatch ratio >1.4). The 90-day good functional outcome rate in MR RESCUE was also much lower in comparison to other trials, and similar to the No Target Mismatch group of DEFUSE 2 (mRS 0–2 in 23 % vs. 22 – 25 %) [35]. Finally, all three studies had long periods of enrollment and difficulty in the recruitment of patients, resulting in a small number of patients per center-year [36].

The limitations cited for these trials make it difficult for clinicians to generalize the data to current stroke treatments.

Phase VI: "All truths are easy to understand once they are discovered; the point is to discover them." – Galileo Galilei

The important lesson about ischemic stroke treatment is that intra-arterial thrombectomy alone is not the answer for stroke. The FDA approved these endovascular devices to recanalize blood vessels. At some point, this became equated to treatment for stroke. The current literature suggests two critical points: 1) There is no data showing that endovascular treatment is harmful in comparison to standard therapies. 2) Endovascular treatment may simply be the first step to restoring the injured brain.

The question then arises as to when interventional therapy for acute ischemic stroke would be most beneficial. The recent clinical trials cannot address the role of thrombectomy devices for patients beyond the therapeutic window for IV t-PA or for patients ineligible for IV t-PA, although the PROACT-II trial indicated a benefit [30•]. Prudent patient selection and improved stroke processes for rapid administration of endovascular therapy may be the most important variables for attaining clinical efficacy.

Data suggest that endovascular treatment may be beneficial to some patients with target DWI/PWI mismatch, adequate collateral perfusion, and high NIHSS presentations due to large vessel occlusions [33•, 35]. An IMS III subset analysis showed that patients with large vessel occlusions benefit from IA therapy, even considering a long lag time to therapy and inferior technical performance of first generation devices [34]. Other studies have demonstrated that stent-based thrombectomy results in better outcomes in large vessel occlusions compared to IV thrombolysis in acute middle cerebral artery occlusion [37]. In the words of the IMS III authors, a difficult dilemma is treating patients that have received IV t-PA and harbor a large vessel occlusion [38]. Ideally, the patient would be treated in a future clinical trial comparing IV t-PA and combination therapy with emphasis on shorter times to endovascular therapy. If that is not possible, physicians may consider providing immediate endovascular therapy to patients with terminal ICA or basilar occlusions, and consider endovascular therapy for patients with M1 middle cerebral artery occlusions who are not improving within the first 30 min of IV t-PA therapy.

The new generation of flow restoration devices (Solitaire, Trevo) have proven to be far superior to the Merci device with respect to both recanalization rates and speed of recanalization [39]. These promising devices need to be validated through robust randomized trials to reconcile the gap between high rates of recanalization and clinical efficacy.

As we move forward, our focus may shift to neuroprotection in combination with interventional therapy. Neuroprotection helps prevent ischemia and reperfusion injury through the inhibition of apoptosis, oxidative stress and inflammation. Besides decreasing time to treatment, therapies involving glucose control and temperature reduction are currently being explored, such as through the Stroke Hyperglycemia Insulin Network Effort SHINE trial (a multicenter, randomized trial evaluating whether glucose control with intravenous insulin results in improved functional outcomes in acute ischemic stroke patients) [40].

New neuroprotective compounds guard the brain from focal cerebral ischemia. For instance, Human-Derived Physiological Heat Shock Protein 27 (hHSP27) has been shown to be a strong cell death suppressor in animal models [41]. Although there are many compounds that are effective in animal models, there needs to be further translational research to clinically validate human neuroprotective treatments. For example, over 1,000 presumed neuroprotective agents have been developed in animal models and over 100 drugs have advanced to clinical trials, but none have demonstrated clinical efficacy [42].

Recanalization of occluded vessels may be the first step in "opening the bridge" to deliver neuroprotective agents and possibly regenerative therapies such as stem cells to the injured brain. Time to treatment following acute ischemic stroke is critical. Conversely,

using imaging techniques to identify areas of salvageable tissue, neuroprotective agents may alternatively function to stabilize the ischemic penumbra while trying to establish reperfusion [43].

Conclusion

Phase VII: "The best thing about the future is that it comes one day at a time." – Abraham Lincoln

Over the past 20 years, the treatment for ischemic stroke has rapidly evolved with the advent of new imaging technologies, thrombolysis and endovascular interventions. In this new age, we must support investigators to provide more conclusive data on patient selection criteria, improvement of stroke intervention processes, and the clinical efficacy of the newest generation of thrombectomy devices. As we focus on minimizing time to treatment, advancing endovascular device technology, and expanding our knowledge of neuroprotective and regenerative therapies, the treatment for ischemic stroke will be continue to progress, hopefully resulting in improved patient outcomes.

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Alex Y. Lu, Dr. Sameer A. Ansari, Dr. Karin V. Nyström, Dr. Eyiyemisi C. Damisah, Dr. Hardik P. Amin, Dr. Charles C. Matouk, Rashmi D. Pashankar, and Dr. Ketan R. Bulsara all declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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