

A review of intra-arterial and intravenous therapies for acute ischemic stroke: relevance, challenges and developments

Abstract

Intravenous and intra-arterial thrombolysis (IVT and IAT, respectively) are the two major therapeutic options for management of acute ischemic stroke (AIS). However, the FDA has only approved IVT for management of AIS, when the patient presents within 0-4.5 hours of AIS onset. This recommendation was based on numerous randomized controlled trials (RCT) which, when analyzed together, showed a net benefit towards the use of IVT. But a narrow therapeutic window, which is rarely met by the individual, and the relative inefficacy of IVT in large artery occlusions, leaves a lot to be desired in the management of AIS. Thus, in these situations, the focus has shifted towards the possibility of using IAT, both pharmacologic and mechanical. Numerous studies have been performed comparing IAT and IVT in treating AIS. None of the major trials found any significant benefit of IAT when compared with IVT. In this review, we compare the efficacy and the relative benefits of both IAT and IVT and discuss the significant findings and limitations of major trials studying these therapies. We suggest that IAT appears as a promising alternative to IVT in specific cases. The lack of benefit observed in major RCTs may have been due to inadequate study designs and execution. Further randomized controlled trials are underway to better understand the role of IAT in AIS.

Keywords: Stroke, Intravenous thrombolysis, Intra-arterial therapy, Review

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Abbreviations: IVT, Intravenous; IAT, Intra-Arterial Thrombolysis; AIS, Acute Ischemic Stroke; RCT, Randomized Controlled Trials; NINDS, Neurological Disorders and Stroke; ICH, Intracerebral Hemorrhage; FDA, Food and Drug Administration; NIHSS, National Institute of Health Stroke Scale; ASK, Australian Streptokinase; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; ATLANTIS, Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; IST-3, Third International Stroke Trial; EPITHET, Echo planar Imaging Thrombolytic Evaluation; PROACT, Prolyse in Acute Cerebral Thromboembolism; EMS, Emergency Management of Stroke; IMS, Interventional Management of Stroke; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; POET, Parameter optimized endovascular treatment

Intravenous therapy for acute ischemic stroke

The National Institute for Neurological Disorders and Stroke (NINDS) trial¹ published in 1995, was a landmark randomized controlled trial that advocated for the use of intravenous tissue plasminogen activator (IV t-PA), in patients with acute ischemic stroke presenting within 3 hours of onset. Patients were randomized to receive placebo or alteplase (0.9mg/kg, up to a maximum dose of 90mg). The trial found a significantly higher odds ratio for favorable outcome in the treatment group (OR 1.7, 95% CI: 1.2-2.6; p=0.008). There was a 32% relative increase in patients with minimal or no disability (Barthel Index score 95 or 100) and a 55% relative increase in the number of patients with National Institute of Health Stroke Scale (NIHSS) between 0-1 in the t-PA group as compared to placebo. There was no significant difference in mortality at 90 days (p=0.30); however, the incidence of symptomatic intracranial hemorrhage in the first 36 hours was higher in the t-PA group (p=0.001). The group

concluded that despite an increase in the incidence of Intracerebral Hemorrhage (ICH) in the early stages, t-PA improved clinical outcome at 3 months when used within 3 hours of onset of acute ischemic stroke. The drug was subsequently approved by the Food and Drug Administration (FDA).²

The study highlighted two main points.¹

- When stratified by time of onset, the outcome varied among the t-PA and the placebo group in 0-90 min and 90-180 min strata (OR 2.1 vs. 1.69)
- The benefit was seen in moderate strokes (NIHSS 6-20) with a insignificant effect on both mild (≤ 5) and severe stroke s (≥ 25) (For an interpretation of NIHSS, please see Appendix 1).

Appendix 1 National Institute of Health Stroke Scale

NIHSS score	Interpretation
≥ 25	Very severe neurological impairment
15-24	Severe impairment
5-14	Moderately severe impairment
< 5	Mild impairment

Adams HP, Davis PH, Leira EC, Chang KC, Bendixen BH, et al. (1999) Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Neurology 53(1): 126-131.

The effectiveness of t-PA in this study was also confirmed by a re-analysis of the same trial data.³ It concluded that the NINDS study supported the use of t-PA within 3 hours of onset of AIS. The committee also stated that the imbalance in the NIHSS scores did not invalidate the finding.

During the same period, the Australian Streptokinase (ASK) trial group and the Multicenter Acute Stroke Trial-Europe (MAST-E) trial group evaluated the efficacy of streptokinase in acute ischemic

stroke.^{4,5} These studies could not find a significant benefit in the use of thrombolysis in AIS and, in fact, found a higher rate of mortality.

The European Cooperative Acute Stroke Study (ECASS) also came up with negative results.⁶ The study concluded that t-PA was effective in improving some functional and neurologic measures in a subgroup of stroke patients with moderate-severe neurologic deficits; however these benefits were masked by an increased incidence of parenchymal hemorrhage in the t-PA group along with a non-significant increase in the group's 30-day mortality. However, the study was criticized for using higher dose of t-PA (1.1mg/kg, up to a maximum of 100mg) in comparison to most other trials and by the significantly higher number of protocol violations in the t-PA group (p=0.03).⁶

In the light of these limitations, the ECASS II was initiated comparing the administration of 0.9mg/Kg t-PA given intravenously within 6 hours of onset of symptoms versus placebo.⁷ The t-PA and the placebo groups did not differ significantly in the incidence of hemorrhagic infarction; however, the incidence of parenchymal hemorrhage was four times more common (12% vs. 3%) in the t-PA group. Although their primary endpoint showed no difference between the t-PA and the placebo group (Modified Rankin Scale (mRS) ≤1 at day 90), a subsequent re-analysis with dichotomized mRS scores (≤2, >2) showed that there were 8.3% more individuals (p=0.024) who were independent (mRS 0-2) in the t-PA group as compared to placebo. The mRS scoring system is detailed in Appendix 2. One of the limitations of the study was that patients in ECASS II had less severe neurologic deficits on entry as compared to both the ECASS I and the NINDS trials, which may have led to a seemingly better placebo response while also masking the effect of t-PA. However, the group found that t-PA at a dose of 0.9mg/kg did not increase morbidity or mortality despite a 2.5 fold increase in symptomatic ICH. The authors of the ECASS II believed that the results supported the use of routine management of t-PA within 3 hours of onset of AIS. The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) trial [8] similarly found that patients treated with t-PA within 3 hours of onset of AIS had a better outcome as measured by NIHSS≤1 (p=0.01). However, there was no benefit observed in either the Modified Rankin Scale or the Barthel Index in between both the groups.

Appendix 2 Modified Rankin Scale (mRS)

mRS Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

http://www.strokecenter.org/wp-content/uploads/2011/08/modified_rankin.pdf

There were concerns as to whether the efficacy demonstrated by t-PA in clinical trials would be carried over to the AIS patient

population in actual clinical settings. A study by Katzan et al.⁹ showed that in practice, the rate of symptomatic ICH was much higher than that seen in the NINDS trial (15.7% vs. 6.4%). This finding was in contrast to another population-based study known as the Standard Treatment with Alteplase to Reverse Stroke (STARS) study.¹⁰ which found the rate of symptomatic ICH to be lower to that of the NINDS trial (3.3% vs. 6.4%). In the former study, there were protocol violations in about 50% of the patients receiving t-PA as compared to 33% in the latter. Although in both the studies, protocol violations were not related to symptomatic ICH, other studies have shown that these events are indeed related to each other.¹¹⁻¹³ The safety and efficacy of administration of t-PA also was demonstrated by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) study.¹⁴

The role of t-PA in the elderly was studied by the third international stroke trial (IST-3).¹⁵ whose findings were published in 2012. The IST 3 was an international, multicenter RCT that studied the effect of t-PA when given within 4.5 hours of stroke onset, especially in the elderly. 3035 patients were enrolled in 156 centers in 12 countries. 53% of the enrolled patients were older than 80 years of age. IST-3 found that the benefit with t-PA treatment was the greatest within 3 hours, and the effect of treatment in patients older than 80 years of age was at least as large as patients who were younger.

Can IV t-PA be administered after 3 hours?

Although this particular line of inquiry this was studied by the ATLANTIS and ECASS II studies, the sample size of each trial was very small and was not powered to detect an effect size of 7-10%. Therefore, speculation on the possible efficacious use of t-PA at more than 3 hours post-stroke remained. The effects of alteplase beyond 3 hours after stroke in both the Echo planar Imaging Thrombolytic Evaluation (EPITHET) trial.¹⁶ and ECASS III studies aimed to address this outstanding issue.¹⁷

EPITHET.¹⁶ studied the effect of t-PA when administered between 3-6 hours after stroke onset. The group found that t-PA was associated with less infarct growth (p=0.001) and significantly higher rates of reperfusion as compared to placebo. However, the study was unable to prove the efficacy of thrombolysis after 3 hours of AIS onset.

ECASS III.¹⁷ aimed to study the efficacy of t-PA between 3-4.5 hours after stroke in 821 patients. ECASS III.¹⁷ was able to demonstrate the efficacy of t-PA up to 4.5 hours after stroke onset. The study met the primary end point (mRS≤1 at day 90; OR 1.42, 95% CI: 1.02-1.98; p=0.04) and the global odds ratio for favorable outcome were 1.28 (p<0.05), indicating that the odds for a favorable outcome (i.e., the ability to return to an independent lifestyle) after stroke was 28% higher with alteplase than with placebo. Although the incidence of ICH was higher in the t-PA group, the investigators did not find any difference in mortality. The group thus concluded that t-PA was safe and effective even when administered between 3-4.5 hours after AIS.

To put all the trials into perspective, a large systematic review was undertaken by Wardlaw et al.¹⁸ The review encompassed 12 RCTs with a total of 7012 patients. It showed a significant increase (p<0.05) in the proportion of patients who were alive with favorable outcomes and alive and independent at follow up when t-PA was administered despite a relative increase in mortality at 7 days. While the review reiterated that the benefit was greatest when t-PA was given within 3 hours of onset of AIS, it also suggested that the benefit of t-PA likely extended beyond 4.5 hours, possibly up to even 6 hours after AIS onset in some cases.

Endovascular therapy for AIS

Although IV t-PA has been accepted as a standard treatment for AIS, a number of issues exist regarding the use of intravenous thrombolysis for that condition:

- a. The narrow 3 hour time window period after AIS onset means that very few patients would be able to present within that time. The penumbra surrounding the infarcted core is viable for many hours after onset of AIS.¹⁹ The DEFUSE 2 study demonstrated that endovascular therapy up to 12 hours of stroke in an individual with a significant penumbra on MRI was associated with a good neurological outcome as compared to individuals whose MRI did not show a significant penumbra.¹⁹
- b. IV t-PA was found to be less effective in large artery occlusions involving the carotid artery, the middle cerebral artery (MCA) and/or the basilar artery.²⁰
- c. Although more effective than placebo, there was still a morbidity and mortality of up to 58% in AIS after the introduction of IV t-PA.^{1,10}

Due to these reasons, it was thought that endovascular therapy would be more promising.

Intra-arterial thrombolysis

The Prolyse in Acute Cerebral Thromboembolism (PROACT).²¹ study was a randomized controlled study designed to reevaluate the safety and efficacy of intra-arterial local delivery of recombinant pro-urokinase (pre-UK) versus placebo. The study found that intra-arterial administration of pro-UK was associated with superior recanalization in AIS as compared to placebo, although there were concerns of symptomatic hemorrhage in the pro-UK group. This study was followed up by PROACT II.²² which was designed to determine the clinical efficacy and safety of intra-arterial administration of pro-UK in patients with acute stroke of less than 6 hours duration caused by MCA occlusion. The study found a significant increase in clinical outcome (mRS 0-2 at 90 days) in the pro-UK group despite an increase in the frequency of early symptomatic intracranial hemorrhage. The study also showed that the therapeutic window for intra-arterial thrombolysis for MCA strokes could extend to at least 6 hours after the onset of stroke.

The following year, the Emergency Management of Stroke (EMS).²³ trial published its results. It studied the feasibility, efficacy and safety of combined intravenous and intra-arterial administration of recombinant t-PA for stroke within 3 hours of onset of symptoms. The group found significantly higher recanalization ($p=0.03$) in the IA/IV group as compared to the placebo/IA group. This pilot study suggested that combined intra-arterial and intravenous thrombolysis was feasible; but it could not demonstrate a higher efficacy of the combined approach compared to IV therapy alone.

The combined IA/IV approach was also studied by the Interventional Management of Stroke (IMS).²⁴ and IMS II.²⁵ whose results were published in 2004 and 2007, respectively. The IMS study.²⁴ found a significantly ($p<0.05$) better outcome (mRS 0-2 at 3 months) as compared to the placebo group of the NINDS trial and a similar rate of intracranial hemorrhage.

Mechanical thrombectomy

The MERCI.²⁶ ²⁷ and the Multi MERCI.²⁷ studies evaluated the safety and efficacy of the Merci Retriever to open occluded

intracranial large vessels within 8 hours of stroke. In the MERCI study.²⁶ recanalization was achieved in 46% of the patients, which was significantly higher than the rates expected by using a historical control (18%; $p<0.0001$). Recanalization was associated with a good clinical outcome at 90 days (mRS ≤ 2 , RR 4.4; $p<0.0001$) and decreased mortality (RR 0.59; $p=0.01$). The incidence of hemorrhage was similar to that of intravenous t-PA use in the NINDS study. The Multi MERCI.²⁷ found a higher rate of recanalization with the L5 retriever (57.3%, new generation) compared to X5/X6 devices (45.5%, old generation). However, this difference was not significant ($p=0.25$). The study also found that pretreatment with intravenous t-PA before thrombectomy was safe.

A prospective, single-arm trial.²⁸ studied the efficacy and safety of the PENUMBRA embolectomy device. The device was able to achieve a recanalization rate of 100% out of which 45% had met the secondary endpoint of achieving a 4-point improvement on the NIHSS or an mRS ≤ 2 at day 30. The sample size was very small (23 subjects) and there was a 10% adverse event rate associated with the device or the procedure. This study was followed up by the PENUMBRA pivotal stroke trial.²⁹ A recanalization rate of 81.6% was achieved with an 11.2% incidence rate of symptomatic hemorrhage (comparable to that observed in the multi-MERCI trial) and a total procedure-related adverse event rate of 12.8%. Thus, the recanalization rates achieved by PENUMBRA were higher than that of MERCI. The study was able to establish the safety and efficacy of the device in recanalization in patients experiencing AIS secondary to large vessel occlusion within 8 hours of symptom onset.

SOLITAIRE and TREVO are second generation embolectomy devices that have been proven to be more effective than the first generation devices. The Solitaire Flow Restoration Device versus the MERCI Retriever in patients with acute ischemic stroke (SWIFT) trial.³⁰ trial found that the Solitaire device achieved significantly better angiographic, safety ($p<0.05$), and clinical outcomes than the Merci Retriever System. The TREVO versus MERCI retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2).³¹ trial demonstrated the superiority of the TREVO device over the Merci Retriever in treatment of patients with large vessel occlusions who are ineligible or refractory to IV t-PA ($p<0.05$).

Randomized controlled trials to support IAT

Encouraged by the data showing the possible efficacy of IAT in AIS, three RCTs were subsequently conducted and the results were published simultaneously in 2013. These were the IMS III.³² the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE).³³ and the Local versus Systemic Thrombolysis in Acute Ischemic Stroke (SYNTHESIS) expansion.³⁴ trials.

The IMS III.³² was an international, phase 3, randomized, open label clinical trial with a blinded outcome, performed to test the approach of intravenous t-PA followed by endovascular treatment, as compared with intravenous t-PA only. The endovascular treatment comprised thrombectomy by various first and second generation devices including the Merci retriever, Penumbra system and Solitaire; or endovascular delivery of t-PA. The mode of endovascular therapy was decided by the specific neurointerventionalist. There was no significant difference between the two groups in terms of overall proportion of patients, with mRS of ≤ 2 (difference of 1.5% points in favor of endovascular therapy; CI: -4.4 to 18.1). There was also no difference in mortality at 7 days or 90 days, incidence of symptomatic

intracerebral hemorrhage or parenchymal hematoma. There was however, an increase in the rate of asymptomatic intracerebral hemorrhage ($p < 0.05$) in the endovascular therapy group.

The MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy).³³ trial was designed as a phase 2b, randomized controlled, open label trial that randomized patients into either the endovascular group [treated with embolectomy] or the group that received standard care (including IV t-PA, if appropriate). The mean mRS score among the two groups did not differ (3.9% vs. 3.9%; $p = 0.99$). When analyzed according to the presence or absence of the penumbral pattern, embolectomy was still not superior to standard care.

The Synthesis expansion study.³⁴ randomly assigned 362 patients with AIS within 4.5 hours after onset, either to endovascular therapy (intra-arterial thrombolysis with t-PA and/or embolectomy) or to IV-tPA alone. The proportion of patients alive at 3 months without disability ($mRS \leq 1$) was similar in both the groups (30.4% vs. 34.8%; $p = 0.16$). There was no significant difference in symptomatic intracranial hemorrhage or the case fatality rate within 7 days, in between the two groups.

Do these results mark the end of IAT for stroke?

IMS III, Synthesis and MR RESCUE did not favor IAT over IV t-PA. However, many have suggested that instead of being the last nail in the coffin for supporting the use of IAT following AIS, these trials instead highlight the feasibility of a RCT involving both IAT and IV-tPA, as well as the difficulties that arise during planning and execution of such trials. Moreover, the negative results of the relevant trials have been attributed to a number of design and execution flaws. A critical review of the three studies by Qureshi et al.³⁵ discussed these issues.

The major issues were identified as follows:

Design

Inadequate sample size: In the IMS III, the sample size was calculated according to the assumption that endovascular treatment would have an absolute increase of 10% in the patients with primary outcome (mRS 0-2 at 3 months) over iv alteplase. The probability of alpha error was 0.05 with a power of 80% for detecting difference in binomial proportions. However, on analyzing previous trials, it seems that the effect was overestimated. On comparing IMS I&II (endovascular therapy following iv alteplase) with the NINDS trial (IV alteplase only), an absolute benefit of only 5% was found (44% vs. 39%, respectively). Similarly, SYNTHESIS calculated the sample size based on an absolute increase of 15% in patients achieving the primary outcome with endovascular therapy. Again, unless the magnitude of benefit was expected to be far greater than that shown by previous trials, the study was unlikely to reject the null hypothesis. The MR RESCUE trial was expecting a relative reduction of about 33% in mean mRS scores in patients treated with embolectomy in the presence of favorable penumbral pattern compared to either standard group or embolectomy in the absence of a penumbral pattern. The magnitude of relative reduction was quite high as compared to their sample size in each group (ranging from 20-34).

Inclusion of patients with minor ischemic deficits: Patients with low NIHSS scores have milder strokes and would generally have a favorable outcome. In the SYNTHESIS expansion trial, 36% of the patients had an NIHSS < 11. The IMS trial.²⁴ found a non-significant trend in towards benefit of endovascular therapy in patients with NIHSS ≥ 20 ($n = 204$; $p = 0.06$), however this was not seen in patients with a NIHSS of 8-19 ($n = 452$; $p = 0.83$). This suggests that

endovascular therapy may be as good as IV t-PA in patients with mild strokes but may have a greater benefit in patients with severe strokes. Had the sample consisted of more patients with NIHSS ≥ 20 , a significant benefit could have been observed.

Lack of confirmation of arterial occlusion: In the IMS III and the SYNTHESIS expansion trials, it was not necessary to confirm arterial occlusion by CT or MR angiography prior to endovascular treatment. In a cohort study of patients with CT demonstrating large artery occlusion.³⁶ IA thrombolysis was associated with higher rates of mRS 0-2 at 3 months than with IV thrombolysis (53% vs. 23% respectively; $p < 0.05$). Confirmation of arterial occlusion prior to inclusion may have helped include patients who were likely to benefit with endovascular treatment

Low dose of alteplase used for IV therapy prior to endovascular treatment: A lower dose of t-PA (i.e., 0.6mg/kg, as compared to 0.9mg/kg) was given via IV route in the IMS III trial before administering IA thrombolysis. This was done to prevent the administration of t-PA in excess of 0.9 mg/kg in total (Intra-arterial (IA)+IV). However, previous studies have shown [36] that there was no correlation between the total dose of t-PA administered and the risk of ICH. In trials evaluating the efficacy of IV t-PA, the drug was administered over 60 minutes. In IMS III the total dose of the drug (IA+IV=0.9mg/kg) was delivered in 4 hours. Due to the short half-life of alteplase, this dosing schedule may have been ineffective. The maximum dosage was increased to 112mg in between the study, but patients receiving alteplase before this amendment may have received an inadequate dose of the drug.

Limited use of new generation devices: Recent studies have shown that newer generation thrombectomy devices (TREVO, SOLITAIRE (TM) etc).^{30,31} are more effective than the first generation devices. In the IMS III trial, 1% of the patients randomized to the endovascular group were treated with SOLITAIRE. In the SYNTHESIS expansion trial, only 13% of the patients randomized to the endovascular group were treated with either SOLITAIRE or TREVO. MR RESCUE did not use the newer generation devices in any of the patients. The infrequent use of these devices may have been the reason for lower recanalization rates observed in the endovascular group, thereby also leading to a non-significant difference between the endovascular and the IV t-PA group

Execution

Low enrollment of patients with posterior circulation distribution ischemic stroke: Endovascular treatment has been preferentially considered in patients with acute basilar artery occlusion due to the high rates of morbidity and mortality seen following the administration of IV alteplase. Strokes localized to the posterior circulation included 2%, 8% and 0% of the populations in the IMS, SYNTHESIS expansion and the MR RESCUE trials, respectively. Such a low enrollment of patients with posterior circulation occlusion may have contributed to the negative results.

Inadequate rates of parameter optimized endovascular treatment in IMS III, SYNTHESIS expansion, MR RESCUE: Parameter optimized endovascular treatment (POET) is an endovascular treatment that achieves high rates of recanalization without a high rate of procedural failures. A combined interpretation of previous studies.^{37,38} suggested that achieving a treatment time of < 225 min and resulting in $\geq 80\%$ rate of recanalization would result in 50% or greater rate of favorable outcomes (mRS 0-2). The rates of recanalization did not meet the thresholds required for POET in IMS III and MR RESCUE.

Inadequate randomization affecting the detection and magnitude of benefit: In the MR RESCUE trial, the embolectomy group had significantly lower rates of Congestive Heart Failure (CHF) (8% vs. 26%) and MI (16% vs. 26%) as compared to the IV t-PA group.¹⁷ The lower rates of factors predicting poor prognosis may have reduced the chances of detecting a meaningful benefit in morbidity and mortality. In the SYNTHESIS expansion study, the rate of dissection was significantly higher (8% vs. 2%) in the endovascular group ($p < 0.05$). A higher rate of dissection may have biased the results towards a poor outcome in the endovascular group.

Conclusion

In conclusion, although IV t-PA has been accepted as standard therapy for acute ischemic stroke in patients presenting within 3–4.5 hours after onset, and may have a possible benefit up to 6 hours post-stroke, IAT appears to be a promising alternative and/or adjunct to the former therapy, despite the fact that the latter has not yet been shown to provide a statistically significant benefit over IV t-PA. As discussed herein, this may be due to a number of possible issues relating to inadequate design and/or trial execution. Ongoing randomized controlled trials such as SWIFT PRIME.³⁹ and POSITIVE.⁴⁰ which are using newer thrombectomy devices, may therefore help us to better understand the potential role of IAT in treating patients with AIS.

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Conflicts of interest

None.

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