

Evolution of endovascular mechanical thrombectomy for acute ischemic stroke

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Abstract

Acute ischemic stroke (AIS) is a common medical problem associated with significant morbidity and mortality worldwide. A small proportion of AIS patients meet eligibility criteria for intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator, and its efficacy for large vessel occlusion is poor. Therefore, an increasing number of patients with AIS are being treated with endovascular mechanical thrombectomy when IVT is ineffective or contraindicated. Rapid advancement in catheter-based and endovascular device technology has led to significant improvements in rates of cerebral reperfusion with these devices. Stentrievors and modern aspiration catheters have now surpassed earlier generation devices in the degree and rapidity of revascularization. This progress has been achieved with no concurrent increase in risk of major complications or mortality, both when used alone or in combination with IVT. The initial randomized controlled trials comparing endovascular therapy to IVT for AIS failed to show superior outcomes with endovascular treatment, but

key limitations of each trial may limit the significance of these results to current practice. While endovascular devices and operator experience continue to evolve, we are optimistic that this will be accompanied by improvements in patient outcomes. This review highlights the major endovascular devices used in current practice and the trials which have investigated their efficacy.

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Key words: Cerebral infarction; Endovascular procedures; Intracranial hemorrhages; Stents; Stroke

Core tip: This review discusses the critical advancements in endovascular device technology for the treatment of acute ischemic stroke. Endovascular mechanical thrombectomy is becoming an increasingly utilized treatment approach for patients in whom intravenous thrombolysis with recombinant tissue plasminogen activator is ineffective or contraindicated. While three recent randomized controlled trials found no benefit of endovascular thrombectomy over intravenous therapy, it is important for clinicians to understand the limitations of these trials and recognize the expected key role of endovascular therapy in the future management of stroke patients.

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INTRODUCTION

The annual incidence of stroke in the United States is approximately 795000^[1]. Stroke is the second leading cause of lost disability-adjusted life-years in high-income

Table 1 Summary of endovascular mechanical thrombectomy devices

Device	Manufacturer	Mechanism
Merci retriever	Concentric Medical	Thrombus retrieved with helical snare
Penumbra system	Penumbra Inc.	Thromboaspiration
Solitaire FR	eV3 Endovascular	Thrombus incorporated into struts of deployed stent
Trevo Pro	Stryker neurovascular	Thrombus incorporated into struts of deployed stent

countries and the second most common cause of mortality worldwide^[2,3]. Approximately 80% of strokes are ischemic and 20% are hemorrhagic^[4]. Acute ischemic stroke (AIS) is caused by a focal interruption of cerebral blood flow, most commonly due to occlusion of a major cerebral artery by local thrombosis or embolus. The resulting ischemia leads to tissue damage through a complex pathophysiological response of excitotoxicity, perinfarction depolarization, inflammation and apoptosis^[5].

The goal of therapy for AIS is to achieve cerebral reperfusion before neurological damage becomes irreversible. The correlation between vessel recanalization and favorable neurological outcome is well-studied^[6,7], although additional factors such as stroke severity and age are also likely to have a significant impact on clinical outcome^[8,9]. Currently, the only FDA-approved treatment with level 1 evidence for AIS is intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (alteplase) within three hours of symptom onset^[10]. Additional trials have demonstrated that extending this time window to 4.5 h is beneficial in appropriately selected patients^[11,12]. However, few patients (< 10%) meet eligibility criteria for this therapy^[13-15]. Additionally, larger and more proximally-located thrombi may be relatively resistant to IVT^[16-21]. Successful recanalization of large vessel occlusion (LVO) with IVT alone is infrequent, ranging from 10% in internal carotid artery (ICA) occlusions to 30% in middle cerebral artery occlusions, and IVT is associated with a risk of systemic and intracerebral hemorrhage (ICH)^[22].

These limitations have led to the exploration of alternative or complementary treatment approaches for AIS. Endovascular mechanical thrombectomy has developed over the past decade as a safe and effective intervention. Rapid advancement in catheter-based and endovascular device technology has led to an increasing number of patients with AIS being treated when IVT is ineffective or contraindicated^[14]. Here, we review the evolution of endovascular mechanical thrombectomy devices for the treatment of AIS.

ENDOASCULAR MECHANICAL THROMBECTOMY

Endovascular treatment of AIS began with intra-arterial (IA) infusion of thrombolytic agents. Several studies investigating these therapies reported favorable rates of vessel recanalization and neurological outcomes^[23-25]. Given the relatively favorable risk to benefit profiles of current mechanical thrombectomy devices, IA thrombolysis

is infrequently used in modern endovascular AIS therapy. This was followed by the implementation of balloon angioplasty and microwire techniques to mechanically disrupt thromboemboli^[26,27]. Additionally, intracranial stents were shown to be effective at restoring blood flow when deployed within an occluded vessel^[28,29].

Endovascular retrieval devices were first developed to recover errant coils and other foreign bodies that had embolized within the cerebral circulation during endovascular procedures^[30-32]. The development of devices to remove occlusive thromboemboli was thus a natural extension of pre-existing technology. Endovascular mechanical thrombectomy involves physical extraction of the thrombus through a catheter. Due to the anatomical limitations imposed by vascular anatomy on currently available thrombectomy catheters, thrombi in large ICA, the Circle of Willis and the first two branches of the anterior (A1 and A2), middle (M1 and M2) and posterior (P1 and P2) cerebral arteries) are the most readily accessible. Smaller branches of the cerebral circulation are often too narrow and tortuous to undergo successful mechanical thrombectomy.

Alternative treatment methods for strokes from LVO are an important development, as medical management is often unsuccessful, and these strokes are associated with high rates of morbidity and mortality^[25]. The two main methods of endovascular mechanical thrombectomy for LVO include: (1) physical grasping and removal of thrombi with retrieval devices and (2) aspiration of occlusive thrombi with suction devices (Table 1).

MERCI RETRIEVER

The Merci Retriever (Concentric Medical, Mountainview, CA) was FDA-approved in August 2004 as the first clot retriever device in the United States. This device utilizes memory shaped nitinol (nickel titanium) material to convert from a straight to helical configuration to grasp the thrombus. In this procedure^[33]: (1) the retriever is advanced through the thrombus in its straight configuration; (2) two to three helical loops are deployed beyond the thrombus; (3) the device is retracted to contact the thrombus, and proximal loops are deployed within the thrombus; (4) a balloon guide catheter located in the common or internal carotid artery is inflated to control intracranial blood flow; and (5) three to five clockwise rotations are performed to fully ensnare the thrombus, and the Merci Retriever-thrombus complex and microcatheter are removed together.

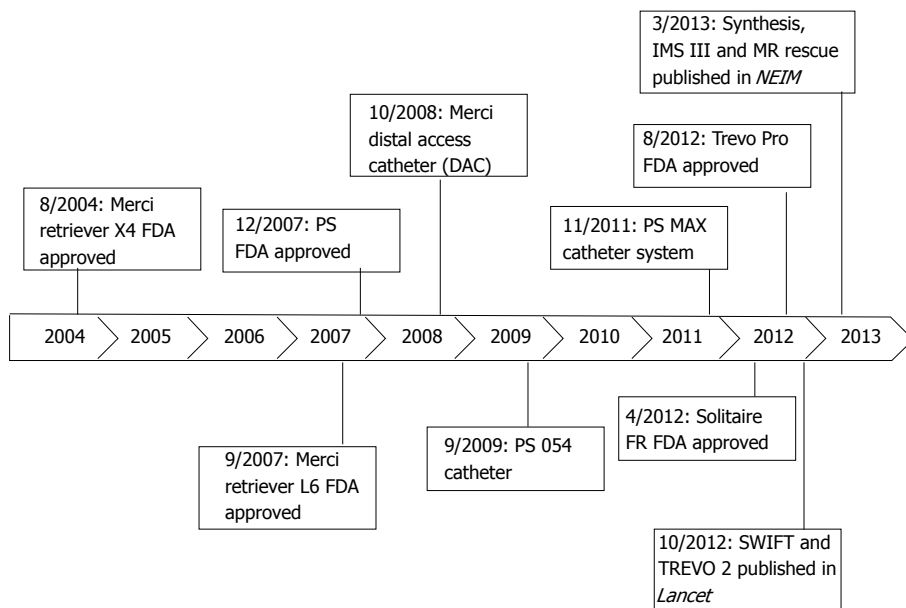


Figure 1 Timeline of FDA approval, release dates and randomized controlled trials of endovascular mechanical thrombectomy devices.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial was a prospective, non-randomized, multicenter trial that first evaluated this device^[34]. Recanalization, defined as Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow in all treatable vessels, was achieved in 48% (68/141) of patients. Patients with recanalization had better neurological outcomes ($P < 0.0001$), as determined by modified Rankin Score (mRS) of 2 or less at 90 d, and lower mortality rates ($P = 0.01$) than those without recanalization, and procedure-related complication and symptomatic ICH rates were comparable to trials of IV t-PA, combined IV/intra-arterial t-PA, and intra-arterial prourokinase^[10,25,35].

Newer device generations (Figure 1) have moderately improved rates of recanalization^[36]. One such advancement was the Distal Access Catheter (DAC; Concentric Medical) in 2008. The DAC has a flexible distal shaft that facilitates its navigation around the anterior genu of the ICA, beyond the origin of the ophthalmic artery^[37]. This improved the navigation of the Merci Retriever through the carotid siphon with each pass, improving procedural efficiency.

PENUMBRA SYSTEM

The Penumbra System (PS) (Penumbra Inc., Alameda, CA) was FDA-approved in December 2007 and utilizes aspiration for thrombus extraction. In this procedure^[38]: (1) the PS catheter is advanced through a guide catheter to a point just proximal to the occlusion; (2) a microwire called a separator is repeatedly passed through the thrombus in order to fragment the clot; and (3) constant suction is applied to the PS catheter to aspirate the thrombus fragments.

The PS was evaluated in a prospective, multicenter study of 125 patients with National Institute of Health

Stroke Scale (NIHSS) score ≥ 8 who were ineligible for or refractory to IVT^[38]. Recanalization (TIMI ≥ 2) was achieved in a high proportion (81.6%) of patients without significantly different complication rates than those seen in the MERCI trials. Good clinical outcome (mRS ≤ 2) was observed in 25% of patients at 30-d follow-up. More recent generations of the PS include the 054 Reperfusion catheter (2009) and the MAX Reperfusion catheter line (2011). These devices achieve greater aspiration force due to larger proximal lumens^[39]. The 054 Reperfusion device was found to accomplish recanalization at a median time of 20 min^[40], significantly less than the median time of 45 min reported in the penumbra pivotal trial using previous generation technology.

STENTRIEVER DEVICES

Stentriever utilize a retrievable stent to engage and remove the thrombus. In this procedure^[41]: (1) the stentriever is advanced within a microcatheter through the thrombus until it is a few millimeters distal to the clot; (2) the stent is deployed, incorporating the thrombus into the stent struts and displacing it radially to the vascular wall; and (3) after three to five minutes, the microcatheter and stentriever are removed together under continuous proximal aspiration with a syringe. This must be performed cautiously, as at least one case of intracranial extravasation during device withdrawal has been reported^[42]. It is also possible to perform a control angiogram while the stentriever is deployed, which can confirm flow restoration. However, since this may promote distal migration of thrombus fragments, the utility of performing an angiogram during stentriever deployment is controversial.

Solitaire FR

The Solitaire FR (eV3 Endovascular, Irvine, CA) was

Table 2 Comparison of randomized trials of endovascular thrombectomy for AIS

Trial	Treatment arms	<i>n</i>	Revascularization ^a (%)	Good outcome ^{bc} (%)	Symptomatic ICH (%)	Mortality ^b (%)
SWIFT	Merci Retriever	55	67	33	11	38
	Solitaire FR	58	89	58	2	17
TREVO 2	Merci Retriever	90	60	22	2	24
	Trevo Pro	88	86	40	4	33
SYNTHESIS ^d	IVT	181	NR	35	6	6
	EVT	181	NR	30	6	8
IMS III	IVT	222	NR	39	6	22
	IVT + EVT	434	e	41	6	19
MR Rescue	Penumbra, IVT	34	93	26	6	21
	Penumbra, EVT	34	67	21	9	18
	Nonpenumbra, IVT	20	78	10	0	30
	Nonpenumbra, EVT	30	77	17	0	20

^aDefined as TIMI or TIC1 grade ≥ 2 a, final revascularization rate including rescue therapies; ^bAssessed at 90 d unless otherwise specified; ^cDefined as mRS ≤ 2 unless otherwise specified; ^dThis study used mRS ≤ 1 as the primary clinical efficacy endpoint and assessed mortality at day 7 \pm 2; ^eReported as 65%, 81%, 70% and 77% for ICA, M1, single M2 and multiple M2 occlusions, respectively; statistically significant ($P < 0.05$); SWIFT: SOLITAIRE™ with the intention for thrombectomy; TREVO 2: Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke; AIS: Acute ischemic stroke; IMS: Interventional Management of Stroke; IVT: Intravenous thrombolysis; ICH: Intracerebral hemorrhage; TIMI: Thrombolysis in Myocardial Infarction; TIC1: Thrombolysis in Cerebral Ischemia; mRS: Modified Rankin Score.

approved by the FDA in March 2012. Initial non-randomized case series with the Solitaire FR demonstrated high rates of recanalization (89%-96%) and improved rates of favorable clinical outcome (mRS ≤ 2 ; 42%-69%) compared to earlier devices^[29,41,43-45]. The Solitaire FR was then directly compared to the Merci Retriever in the SOLITAIRE™ with the intention for thrombectomy (SWIFT) trial (Table 2)^[46]. This was a parallel-group, non-inferiority trial of 113 patients randomized to either the Solitaire ($n = 58$) or Merci ($n = 55$) device. The primary outcome (TIMI ≥ 2) was more likely to be achieved in the Solitaire group than the Merci group (64% *vs* 24%; $P < 0.0001$ non-inferiority; $P = 0.0001$ superiority). Additionally, patients in the Solitaire group were more likely to achieve a good neurological outcome (mRS ≤ 2) at 90 d (58% *vs* 33%; $P < 0.0001$ non-inferiority; $P = 0.02$ superiority) and had a lower 90-d mortality rate (17% *vs* 38%; $P = 0.0001$ non-inferiority; $P = 0.02$ superiority) than those in the Merci group. Subsequent prospective and retrospective studies have continued to demonstrate high rates of vessel recanalization and good clinical outcomes with the Solitaire FR^[47,48].

Trevo Pro

The Trevo Pro (Stryker Neurovascular, Kalamazoo, MI) is another retrievable stent system which was approved by the FDA in August 2012. Similar to the Solitaire FR, the Trevo Pro was found to be superior to the Merci Retriever in a head-to-head randomized study^[49]. The Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke trial assigned patients with AIS from LVO to either the Trevo Pro ($n = 88$) or Merci Retriever ($n = 90$) device. Patients in the Trevo Pro group were significantly more likely to reach the primary outcome, defined as Thrombolysis in Cerebral Ischemia (TICI) grade ≥ 2 , (86% *vs* 60%; $P < 0.0001$ superiority) and achieve a good 90-d neurological outcome (mRS \leq

2; $P = 0.013$) than those in the Merci Retriever group. No significant difference was observed in the safety profile (a composite of symptomatic ICH and procedure-related complications; $P = 0.1826$) or 90-d mortality rates ($P = 0.1845$) of these two devices.

A review of 13 prospective trials endorsed improved rates of vessel recanalization with the newer generation stentriever devices^[50]. While early trials (mainly utilizing IA thrombolysis and the Merci Retriever) reported recanalization rates of approximately 50%, recent trials with stentriever consistently reported rates of approximately 85%. A significantly greater time from symptom onset to endovascular treatment in more recent trials was also observed. This may explain their finding that although vessel recanalization rates have significantly improved over time, functional outcomes remain relatively stagnant. Nevertheless, stentriever and large bore aspiration catheters have become the dominant endovascular devices used to treat AIS in modern practice. A recent prospective trial found no major differences in the efficacy or safety of the Solitaire FR and Trevo Pro^[51].

COMBINED SUCTION EMBOLECTOMY AND MECHANICAL RETRIEVAL

The MAX reperfusion catheters allowed for the development of direct aspiration as an additional thrombectomy technique. Direct suction can be applied from the PS device or a syringe plunger connected to the proximal hub of the catheter. Previously, this technique was limited by the challenges of tracking an aspiration catheter through the intracranial circulation, but the improved trackability of the MAX reperfusion catheters has facilitated its development^[57]. Furthermore, these catheters can still be used in combination with other endovascular devices. The ADAPT technique^[52] is an increasingly utilized ap-

proach which combines modern aspiration and retrieval technology. Direct aspiration with a large bore aspiration catheter (commonly MAX reperfusion system) is first performed. If direct aspiration fails, stentriever, balloons and stents can be still be passed through the catheter. A recent retrospective series of 98 patients by Turk *et al*^[53] reported revascularization (TICI \geq 2b) in 78% of cases following direct aspiration. When stentriever were used following failed direct aspiration, this rate rose to 95%, a previously unparalleled result.

Penumbra 3D separator

The Penumbra 3D Separator is the newest generation PS device currently being investigated in randomized controlled trials. It is designed to combine stentriever and direct aspiration technology into a single device. The new separator device is configured similarly to a stentriever, with an additional radial dimension to fragment the clot under continuous direct aspiration. The stent struts are designed to minimize vessel contact and thus theoretically reduce iatrogenic injury to the endothelium. An initial prospective study of 20 patients treated with the Penumbra 3D Separator demonstrated vessel recanalization (TICI \geq 2b) and favorable neurological outcome (mRS \leq 2) in 85% and 50% of patients, respectively^[54].

ENDOASCULAR THERAPY VS IVT FOR AIS

Due to the promising results from early pilot trials of endovascular mechanical thrombectomy for AIS^[55,56], randomized controlled trials were undertaken to evaluate the benefit of endovascular therapy compared to IVT in a more rigorous fashion.

IMS III

The Interventional Management of Stroke (IMS) III trial^[57] randomly assigned 656 patients who had received IVT within three hours of AIS symptom onset to receive additional endovascular therapy ($n = 434$) or IVT alone ($n = 222$) in a 2:1 ratio. In the endovascular group, 330 patients received treatment: IA thrombolysis alone ($n = 160$), mechanical thrombectomy alone ($n = 57$), IA thrombolysis plus mechanical thrombectomy ($n = 97$) and combinations of multiple mechanical thrombectomy devices with or without IA thrombolysis ($n = 16$). There was no significant difference between the endovascular and IVT groups for achieving a 90-d mRS \leq 2 (40.8% and 38.7%, respectively; 95%CI: -6.1 to 9.1). Additional subgroup analyses showed no difference between the two groups in patients with NIHSS \geq 20 (95%CI: -4.4 to 18.1) or NIHSS $<$ 20 (95%CI: -10.8 to 8.8). Similar rates of symptomatic ICH (6.2% in the endovascular group and 5.9% in the IVT group; $P = 0.83$) and 90-d mortality (19.1% in the endovascular group and 21.6% in the IVT group; $P = 0.52$) were observed.

Enrollment and treatment of patients in the endo-

vascular arm of this trial was not optimal. Over 20% of patients in the endovascular arm were included for analysis despite not receiving any endovascular therapy (due to lack of LVO on angiography). Notably, subgroup analysis of patients with LVO confirmed by CTA showed that endovascular therapy was associated with better functional outcomes than IVT alone ($P = 0.01$)^[58]. The time to endovascular treatment was also significantly longer in the IMS III trial compared to the previous IMS I and II trials. These earlier trials demonstrated that there is a close association between time to reperfusion and neurological outcome, with a linear decrease in probability of good neurological outcome with time^[59]. Thus, this treatment delay may have reduced the clinical benefit of endovascular therapy in this trial. Lastly, of those treated, less than 5% were treated with stentriever, either alone or in combination with other devices. This likely contributed to only 40% of patients achieving TICI grade 2b or 3 vessel recanalization^[60].

SYNTHESIS Expansion

The SYNTHESIS Expansion trial^[61] randomly assigned 362 patients with AIS within 4.5 h of symptom onset to either endovascular therapy ($n = 181$) or IVT ($n = 181$). Patients in the endovascular group who underwent treatment ($n = 165$) received either IA thrombolysis ($n = 109$) alone or in combination with mechanical thrombectomy ($n = 56$) without any prior IVT. Survival-free disability (mRS \leq 1) at 90 d, adjusted for key variables (age, sex, initial NIHSS grade and history of atrial fibrillation) did not significantly differ between the endovascular and IVT groups (30.4% and 34.8%, respectively; $P = 0.16$). Secondary outcomes including NIHSS score \leq 6, neurological deterioration, mortality, symptomatic ICH, and recurrent AIS also did not significantly differ between groups.

Again, the protocol of this trial likely resulted in enrollment of patients who were not suitable candidates for endovascular therapy under current recommendations. No preoperative imaging was required to confirm LVO prior to randomization, and a significant portion of patients ($>$ 33%) had a NIHSS \leq 10. Additionally, the majority of patients in the endovascular arm received interventions that would no longer be considered standard of care. Only 13% of patients in the endovascular arm were treated with stentriever^[62], while 60% were treated with IA thrombolysis alone without mechanical retrieval. Because vessel recanalization rates were not reported, it is unclear if these patients received optimal therapeutic effect.

MR Rescue

The MR Rescue trial^[63] randomized 118 patients with large vessel anterior circulation strokes to either mechanical thrombectomy ($n = 64$) or IVT ($n = 54$) within eight hours of symptom onset. Patient groups were also stratified based on pre-treatment imaging into favorable or non-penumbra patterns. Some studies have suggested that measuring the extent of salvageable brain tissue or ischemic penumbra on preoperative imaging may identify

patients who could preferentially benefit from endovascular therapy^[64-67]. Favorable penumbral pattern was defined as a predicted infarct core of 90 mL or less and a proportion of infarct tissue within the at-risk region of 70 mL or less after pre-treatment magnetic resonance imaging or computed tomography. Results showed no significant difference in mean 90-d mRS observed among groups, both in the overall cohort ($P = 0.99$) or when stratified based on penumbral pattern (favorable, $P = 0.23$; non-penumbral, $P = 0.32$). No differences in the rates of symptomatic ICH ($P = 0.24$) or mortality ($P = 0.75$) were observed between groups. These results correlate with findings from a recent study which showed that a non-perfect preoperative ASPECT score did not significantly affect functional outcome^[68].

No patients in the endovascular arm of the MR Rescue trial were treated with stentrievers. Similar to IMS III, this likely contributed to the low overall rate of recanalization. Only 27% of patients in the endovascular arm achieved recanalization of TICI grade 2b or 3^[60]. Additionally, this trial may have been underpowered due to the relatively low number of patients in each group.

Conclusions from Randomized Trials

While these trials provided valuable preliminary data for the assessment of endovascular intervention for AIS, each had significant limitations^[60,62]. In SYNTHESIS and IMS III, patients with LVO were not appropriately selected based on preoperative imaging. In all three trials, due to the pace of advancement in endovascular technologies, a minority of patients were treated with the most modern endovascular devices. Stentrievers were used infrequently in all three studies, which resulted in vessel recanalization rates below current standards. There is evidence that recanalization is associated with improved functional outcomes and reduced mortality^[7]. Thus, the generalizability of the results from these trials to modern endovascular stroke practice is limited, and future randomized controlled trials are still needed.

As supported by the subgroup analysis of patients with CTA-positive LVO from the IMS III trial, evidence still supports the use of endovascular mechanical thrombectomy for LVO within eight hours of symptom onset. Importantly, none of these trials raised questions about the safety of endovascular therapy. Recanalization is now possible in over 80% of cases, and for many patients, endovascular therapy is the only available treatment option. As endovascular devices and operator experience continue to evolve, improvements in patient outcomes are expected. Future trials will need to focus on proper patient selection and achieving optimal therapeutic effect (vessel recanalization) with modern endovascular devices^[69]. Three ongoing clinical trials (THERAPY, SWIFT-PRIME, and POSITIVE) appear to have incorporated these key principles into their study design.

physical extraction of an occluding thromboembolus *via* grasping devices and/or direct/indirect aspiration. Over the past decade, advancements in catheter-based and endovascular device technology have led to strong improvements in rates of vessel recanalization. Initial randomized trials failed to show benefit of endovascular therapy over IVT, but limitations in study design have abated widespread acceptance of their conclusions. Future randomized trials evaluating endovascular mechanical thrombectomy for AIS will need to enroll and treat patients based off of the currently accepted standards of care.

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CONCLUSION

Endovascular mechanical thrombectomy involves the

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