Topical Review

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Techniques for Endovascular Treatment of Acute Ischemic Stroke

From Intra-Arterial Fibrinolytics to Stent-Retrievers

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Early recanalization of occluded vessels in acute ischemic stroke (AIS) either by intravenous thrombolysis or endovascular revascularization has been shown to be associated with improved clinical outcome and reduced mortality.[1] Initial works on endovascular treatment (EVT) of AIS was published in the 1980s.[2,3] Since then, the endovascular techniques for AIS treatment have tremendously improved, advancing from intra-arterial administration of thrombolytic drugs to first-generation mechanical thrombectomy devices (Merci clot retriever and Penumbra clot aspiration) and more recently to second-generation mechanical thrombectomy devices (stent-retrievers; Figure 1). Introduction of various tools and techniques in EVT for AIS will, for obvious reasons, affect the efficacy and safety.

On the other hand, intravenous thrombolysis was evaluated in several large randomized trials and was shown to improve clinical outcome at 90 days if treatment was initiated within 3 hours of stroke onset.[4] Subsequently, the European Cooperative Acute Stroke Study (ECASS) III showed the benefit of intravenous thrombolysis between 3 and 4.5 hours.[5] After establishing the efficacy of intravenous recombinant tissue-type plasminogen activator (r-tPA) in the treatment of AIS, EVT had to be evaluated against intravenous treatment. A long time elapsed before the results of the first randomized controlled trials were published in 2013 demonstrating no major difference between intravenous r-tPA treatment and EVT for AIS.[6–8] Noteworthy, these trials had several limitations including the fact that all EVT were approved for use.[9,10]

However, the positive results of Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial and potential results of other trials including Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) and Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) will potentially introduce important modifications in the management of AIS.[11] A precise analysis of these trials will be necessary to determine the place and indications of EVT. Optimizing the selection of patients and EVT procedures will still be an important goal that will have to be evaluated in further trials. Refinement of EVT needs to perfectly understand the different EVT techniques, which were proposed along the time and to analyze their success or failure.

This comprehensive review has the goal to describe precisely the different EVT for AIS treatment analyzing recanalization rates, complications, and clinical outcome.

Early EVT Concepts

In early 1980s, EVT in AIS was based on the intra-arterial and supraselective administration of thrombolytic agents in to the clot. Nonrandomized case series showed the potential clinical benefits of such treatment. Subsequently, the Prolyse in Acute Cerebral Thromboembolism (PROACT) trial, studying a homogeneous population of patients with M1 and M2 occlusions, confirmed the safety and efficacy in term of recanalization of intra-arterial thrombolysis with prourokinase ≤6 hours after onset of neurological symptoms.[12] PROACT I also demonstrated that heparin dose influence hemorrhage frequency and recanalization. PROACT II included 180 patients with AIS associated with a proximal middle cerebral artery occlusion ≤6 hours after onset of neurological symptoms that randomly received 9 mg of intra-arterial prourokinase (121 subjects) or placebo (59 subjects).[13] The rate of good clinical outcome was significantly higher with intra-arterial prourokinase (40%) when compared with that with placebo (25%; P=0.04), despite a higher rate of symptomatic intracranial hemorrhages after intra-arterial prourokinase (10% compared with 2% in the placebo group; P=0.06).

Evaluation of other drugs including glycoprotein IIb–IIIa inhibitors was relatively limited. Intra-arterial administration of glycoprotein IIb–IIIa inhibitor eptifibatide was evaluated in a short series of patients showing that it was a feasible option for salvage of reocclusion and thrombolysis of distal inaccessible thrombi.[14] However, intravenous trials were not able to demonstrate the efficacy of abciximab versus placebo, and intravenous abciximab was associated with an increased rate of intracranial hemorrhage.[15]

The positive results of PROACT II stimulated the development of alternative techniques with the goal not just to dissolve the clot, but expedite the revascularization and to disrupt the clot.

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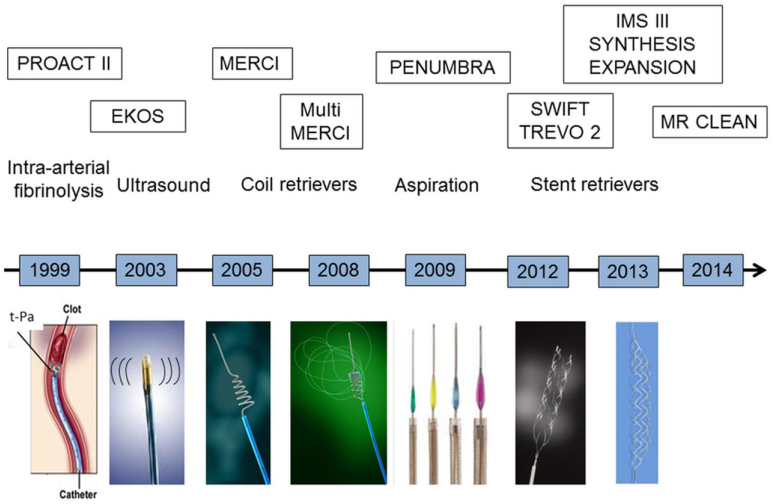

Figure 1. Evolution of endovascular techniques for acute ischemic stroke and clinical trials. IMS indicates Interventional Management of Stroke; MERCI, Mechanical Embolus Removal in Cerebral Ischemia; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; PROACT, Prolyse in Acute Cerebral Thromboembolism; SWIFT, Solitaire With the Intention for Thrombectomy; and TREVO, Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke.

Several methods were initially proposed using tools not dedicated to AIS including injection of saline within the clot through a microcatheter, microwire manipulations of the clot, balloon angioplasty, and manual aspiration of the thrombus. None of these techniques were precisely evaluated in larger studies.

Another approach proposed, which used a combination of intra-arterial thrombolytics and ultrasound to disrupt the clot, using the EKOS system (EKOS, Bothell, WA).[16] Interventional Management of Stroke (IMS) II study was designed to evaluate efficacy and safety of combining low-dose intravenous r-tPA followed by delivery of additional intra-arterial r-tPA in the setting of low-energy ultrasound via the EKOS catheter.[16] Comparison with IMS I results, in which EKOS catheter was not used, showed that in IMS II, the EKOS catheter performed similarly to a standard microcatheter.[17] In IMS III, the use of EKOS microcatheter was limited (6.6% of the 334 patients who received EVT).[6]

The approval of intravenous administration of r-tPA for the treatment of AIS prompted discontinuation of some trials dealing with intra-arterial administration of thrombolytics.[18]

First Generation of Clot Retrievers

In 2004, the Merci retriever (Concentric Medical, Mountain View, CA) was the first device cleared for removal of thrombus from intracranial arteries by the Food and Drug Administration (FDA) based on the 510K pathway (Table 1). The Merci retriever has undergone considerable redesigning along the time, but all versions were preferably used in conjunction with an 8- or 9-F balloon guiding catheter to reduce the risk of distal emboli (see below).

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and multi-MERCI trials were prospective, nonrandomized, multicenter, and single-arm trials designed to test the safety and efficacy of MERCI device in patients presenting with moderate to severe stroke (National Institutes of Health Stroke Scale score ≥8) from a large-vessel occlusion and treated within 8 hours of symptom onset.[19,20] Results of these trials are shown in Table 1.

In 2008, the Penumbra clot aspiration system (Penumbra, Inc, Alameda, CA) was the second device for AIS that was cleared by the FDA. This device enables a thrombus aspiration by use of a large lumen catheter positioned in contact with the clot and attached to a vacuum pump.[21]

The Penumbra suction thrombectomy system was cleared based on results from a prospective single-arm multicenter study (Penumbra Pivotal Stroke Trial) that evaluated the safety and efficacy of the device in 125 subjects treated within 8 hours of stroke symptom onset (Table 1).[22] After the Penumbra device clearance in the United States and Europe, a postmarketing study, analyzed the experience with the Penumbra system outside a trial setting (Table 1).[23]

Second Generation of Mechanical Thrombectomy Devices (Stent-Retrievers)

In vitro and in vivo studies showed that nondetachable neurovascular stents could be used for foreign body and clot removal.[24] The primary function of detachable stents was to assist coiling of intracranial aneurysms or support revascularization of intracranial stenosis in a subset of patients. Detachable stents can be detached from the pusher used to place the stent in the vasculature and then delivered in the cerebral arteries on the contrary to nondetachable stents (including stent-retrievers) that are temporarily placed in the vasculature, but removed after use. Because of its frequent and successful off-label use, the detachable Solitaire intracranial stent (Covidien/EV3; Plymouth, MN) turned into a primary clot retriever (Figure 2).

Table 1. Summary of Main Studies on First-Generation Clot Retrievers

	Devices	Patients	TIMI II/III, %	mRS≤2, %	Hemorrhage, %	Mortality, %
MERCI	Merci	151	46.0	25.0	7.8	43.5
Multi-MERCI	Merci	177	68.0	36.0	9.8	34.0
Penumbra	Penumbra	125	81.6	25.0	11.2	32.8
Penumbra-POST	Penumbra	157	87.0	41.0	6.4	20.0

MERCI indicates Mechanical Embolus Removal in Cerebral Ischemia; mRS, modified Rankin Scale score; and TIMI, thrombolysis in myocardial infarction scale.

Table 2. Summary of Main Studies on Second Generation of Clot Retrievers (Stent-Retrievers)

Study	Devices	Patients	Intravenous r-tPA, %	Recanalization, %	mRS≤2, %	sICH, %	Mortality, %
SWIFT	Solitaire	58	33	61*	37	2	17
STAR	Solitaire	202	59	79.2†	57.9	1.5	6.9
TREVO	TREVO	60	60	91.7‡	55	8.3	20
TREVO 2	TREVO	88	58	92‡	40	7	33
NASA registry	Solitaire	354	45	87.5‡	42	9.9	30.2

mRSA indicates modified Rankin Scale score; NASA, The North American Solitaire Stent-Retriever Acute Stroke; r-tPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracranial hemorrhage; STAR, Solitaire Flow Restoration Thrombectomy for Acute Revascularization Thrombectomy; SWIFT, Solitaire With the Intention for Thrombectomy; TICI, thrombolysis in cerebral infarction scale; TIMI, thrombolysis in myocardial infarction scale; and TREVO, Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke.

*TIMI 2–3, †TICI 2b-3, ‡TICI 2a-3.

Stent-retrievers for AIS combine 2 mechanisms of action are as follows: (1) the deployment of the stent-retriever within the clot immediately restores blood flow and (2) the mesh of stent-retriever embedded within the clot serves to catch and retrieve the clot. Several passes with the stent-retriever, which is delivered, to the occluded site through a microcatheter are infrequently necessary.

Initial single-center followed by larger multicenter case series showed a good device efficacy and clinical outcome with acceptable safety profile specifically in terms of intracranial hemorrhage.[25–29] Subsequently, comparative randomized trials were conducted to evaluate efficacy and safety of first and second generation of devices (Table 2). In the Solitaire With the Intention for Thrombectomy (SWIFT) trial, 58 patients were treated with Solitaire, whereas 55 subjects were enrolled in to the Merci arm.[25] The primary end point defined as a successful recanalization without symptomatic intracranial hemorrhage was achieved in 61% of patients treated with Solitaire and 24% of patients treated with Merci (P=0.0001). Good neurological outcome was observed in 58% of patients treated with Solitaire and in 33% of patients treated with Merci (P=0.017). Symptomatic intracranial hemorrhage was reported in 2% of patients treated with Solitaire and 11% of patients treated with Merci (P=0.057). Death from any cause at 90 days was more frequent in patients treated with Merci (38%) when compared with those treated with Solitaire (17%; P=0.02). The Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO) 2 trial showed similar results.[28]

However, stent-retrievers have potential drawbacks that have to be evaluated in prospective series including anterior cerebral artery emboli (when treating middle cerebral artery or internal carotid artery occlusions), vessel wall damage, and challenges associated with tortuous aortic arches, cervical, or intracranial arteries.

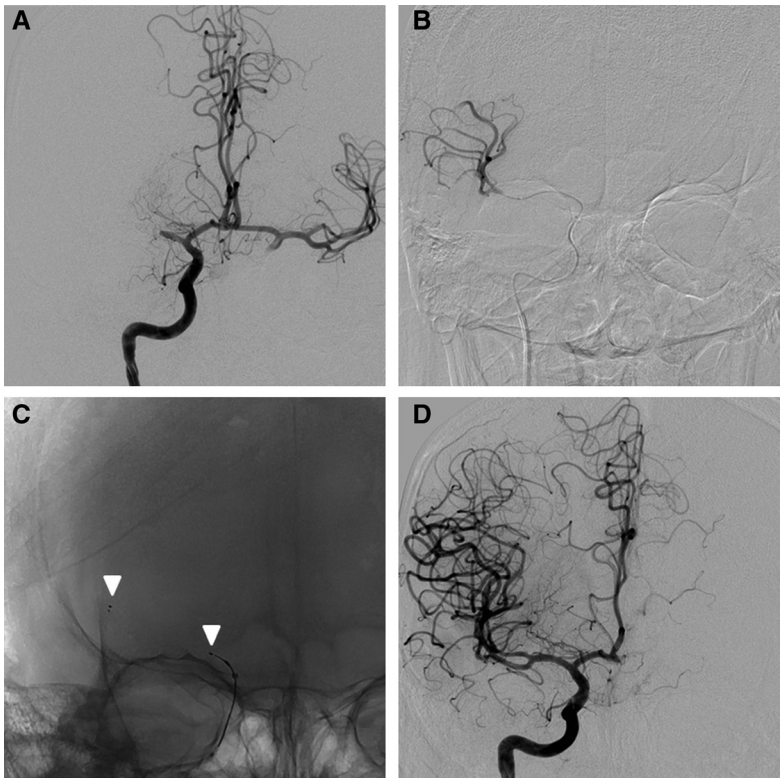

Figure 2. Acute ischemic stroke and stent-retriever mechanism of action. **A**, Digital subtraction angiography shows a middle cerebral artery occlusion. **B**, Superselective injection through the microcatheter placed distally to the clot. **C**, Deployment of the stent-retriever into the clot (arrows show the distal and proximal markers). **D**, End of the procedure: the middle cerebral artery is reopen.

Further technical refinements have also to be evaluated to determine their value, efficacy, and safety in the management of AIS. As shown in vitro and in vivo experimental studies and clinical setting, the use of a balloon guiding catheter placed in the internal carotid artery may be helpful to reduce distal emboli.[30] A balloon guiding catheter has a balloon placed at its distal end on the outer surface. The balloon is inflated during thrombectomy to arrest or reverse the flow and allows aspiration of blood during the clot retrieval process. However, placement of commercially available balloon catheters can be challenging in extreme tortuous carotid arteries or atheromatous lesions. In Solitaire Flow Restoration Thrombectomy for Acute Revascularization Thrombectomy study, the use of a balloon guide catheter was mandatory.[26] The rate of successful recanalization (TICI ≥2b) was high (84.4%) with a high rate of good clinical outcome (modified Rankin Scale score [mRS] ≤2) at 90 days (57.9%). As discussed by the authors, these good results may be associated with several factors and not exclusively related to the device used. Analysis in The North American Solitaire Stent-Retriever Acute Stroke registry showed that the use of a balloon guide catheter (versus no balloon guide catheter) was associated with a shorter procedure time (120 versus 161 minutes; P=0.02), a higher rate of TICI 3 recanalization (53.0% versus 32.5%; P<0.001), and a higher rate of good clinical outcome (51.6% versus 35.8%; P=0.02).[31] Surprisingly, distal emboli and emboli in new territory were similar in both groups.

Application of aspiration pump or vacuum syringe during retrieval of the stent has been performed in most case series with the benefit of reducing number of distal emboli and increasing the amount of clot harvested. Manual aspiration combined with thrombectomy has been a useful addition to the armamentarium of EVT for AIS.[32] Superiority of a pump aspiration has not been demonstrated.

The introduction of large bore and flexible aspiration catheters has prompted the development of a new technique called a direct aspiration first pass technique (ADAPT). The catheter (usually a 5 MAX or 5 MAX ACE; Penumbra, Oakland, CA) is engaged into the clot, a vacuum is applied with a 20- or 60-mL syringe or an aspiration pump, and the clot is pulled out. In 1 case series that included 98 patients, self-reported TICI 2b/3 flow was observed in 75% of treated patients.[33] Notably, distal emboli could not be prevented using the ADAPT technique and were encountered in 10% of cases. Good clinical outcome (mRS, 0–2) at 90 days was obtained in 40% of patients with a mortality of 20%. A recent single-center, retrospective comparison of ADAPT and stent-retriever showed similar recanalization rates (TICI 2b/3) in both groups (ADAPT, 78%; stent-retriever, 80%).[34] Combined with other techniques including stent-retriever for ADAPT, the rate of recanalization was slightly higher in ADAPT group (95.3% versus 83.3% in stent-retriever group). The clinical outcome at 3 months was similar in both groups (ADAPT, 46.7%; stent-retriever, 43.3%). The results of these studies show the potential value of this technique, but they have several limitations, such as their retrospective design, absence of independent assessment of the recanalization status, and small number of patients.

A recent single-center series showed that recanalization with TICI 2b/3 was obtained in only 43% of cases with ADAPT only and in 87.5% with a combination of ADAPT and stent-retriever.[35]

First, it seems useful to prospectively evaluate the safety of this technique in large cohort of patients. Second, a proper randomized controlled trial is needed to evaluate the role of this technique for AIS, like it has been done before with the stent-retrievers, now validated as the most effective technique.[25,28] ADAPT and stent-retriever may be complementary tools to improve recanalization and clinical outcome in AIS.[36] This association (rather than competition) must be considered in the future, and it may be interesting to compare prospectively the usefulness of a combined strategy (ADAPT+stent-retrievers) versus stent-retrievers alone.

Several stent-retrievers are now available with various designs and there are no data available comparing their efficacy and safety profile.

Time-to-Reperfusion and Strategy of Treatment

Analysis of IMS III data showed that delays in time-to-angiographic reperfusion lead to a decreased likelihood of good clinical outcome in patients after moderate to severe stroke concluding that rapid reperfusion could be crucial for the success of future acute endovascular trials.[37] Indeed, rapid reperfusion is also crucial in the current management of patients with AIS.

For future trials and current management, it is crucial to reduce the delay between symptom onset and reperfusion (time-to-reperfusion). In IMS III, EVT was substantially delayed (208 minutes) compared with intravenous (121 minutes), which partially explain the negativity of this study. All steps of the patient's management have to be shortened including the initiation of mechanical thrombectomy. The concept of mechanical thrombectomy as a rescue technique is probably over after the recent results of randomized trials and mechanical thrombectomy has probably to be started as rapidly as possible also when it is associated with intravenous r-tPA.

Conscious Sedation and General Anesthesia

Conscious sedation (CS) and general anesthesia (GA) are used in AIS intervention depending of several factors including patient's clinical status, operator's experience, and availability of anesthesia team.

In a cohort of 980 patients, patients placed under GA during EVT for anterior stroke circulation have a higher chance of poor neurological outcome and mortality when compared with intervention performed under CS.[38] Jumaa et al[39] reported similar results in a series of 126 patients showing a better clinical outcome (mRS≤2) in nonintubated patients (46%) when compared with results in intubated patients (23%; P=0.009). In-hospital death was also lower in nonintubated patients (22% versus 43% for intubated patients; P=0.010).

A case series showed that mechanical thrombectomy with Solitaire stent-retriever was feasible under CS in a high percentage of cases (86.1%) obviating the need for GA in most circumstances.[40] EVT failed because of patient cooperation in 8.3% and to vessel tortuosity in further 2 cases (5.6%). Despite relatively low recanalization rates (77.8%), a high percentage of good clinical outcome at 3 months was reported (61.1%).

In The North American Solitaire Stent-Retriever Acute Stroke registry, GA was used in 69.8% of patients.[41] The clinical outcome favored CS (mRS≤2 seen in 52.6% of subjects treated under CS versus 35.6% of patients treated under GA; odds ratio, 1.4 [1.1–1.8]; *P*=0.01).

The recently published Society for Neuroscience in Anesthesiology Expert Consensus Statement has proposed the following recommendations.[42]

- GA is recommended in patients who are already intubated for medical reasons and for uncooperative patients and most patients with posterior circulation strokes.
- Local anesthesia with sedation and GA are feasible options for cooperative patients who can protect their airway.
- In all patients receiving local anesthesia with sedation, the anesthesia provider should be prepared to rapidly convert to GA if needed.

Periprocedural Management

The Expert Consensus Statement has proposed some recommendations for the perioperative management of patients with AIS treated with mechanical thrombectomy.[42]

Hemodynamic monitoring and management should be started as soon as diagnosis of AIS has been made. Systolic blood pressure should be maintained >140 mm Hg (fluids and vasopressors) and <180 mm Hg and diastolic blood pressure <105 mm Hg.

Heparin is used during the procedure to reduce catheter-induced embolic and thrombotic events. Heparin dosing may be initiated after the decision to treat an intra-arterial thrombus by EVT has been made. Heparin administration (repeat boluses or infusion) is typically stopped at the end of the procedure without reversing the heparin with protamine.

Administration of aspirin is typically withheld for 24 hours after procedure in patients with AIS if thrombolytic therapy was performed. Clopidogrel or aspirin need to be administered during EVT of AIS if an endovascular stent will be permanently placed in the vascular system.

EVT of AIS and Randomized Controlled Trials

The initial randomized controlled trials comparing EVT to intravenous r-tPA were negative, but it was partially explained by their limitations.[6–10] Main weaknesses of these trials were the heterogeneity of the endovascular techniques used (only 1.2% of the patients were treated with stent-retrievers), inappropriate selection of the patients, important delay in the performance of EVT (see above), and small number of patients included per center per year.

In the recently published MRCLEAN trial, in which 97.4% of patients treated by EVT were treated using stent-retrievers, there was an absolute difference of 13.5 percentage points in the rate of functional independence (mRS, 0–2) in favor of the EVT (32.6% versus 19.1%).[11]

The results of other trials (ESCAPE and EXTEND-IA) will be published in the next future and will probably confirm MRCLEAN results. The precise analysis of these trials will be important to understand the place of EVT in the management of AIS and to continue to improve selection of patients and EVT techniques.

Conclusions

Mechanical thrombectomy with stent-retrievers is currently the preferred technique for the endovascular management of AIS. In light of the recent positive MRCLEAN trial and of future results of other trials, the place of mechanical thrombectomy with stent-retrievers in the management of AIS will have to be defined. In parallel improvement of patient selection and refinement of EVT techniques has to be continued and evaluated through appropriate trials.

Disclosures

Dr Pierot is a consultant for Johnson & Johnson/Codman, Covidien/EV3, Microvention/Terumo, Sequent, and Stryker. Dr Wakhloo is a consultant for Stryker Neurovascular, Boston Biomedical Associates and has received research grant from Philips Healthcare. The other authors report no conflicts.

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