



# Endovascular treatment for the acute ischemic stroke: the past and the future

Rui Liu<sup>1\*</sup>, Wei Li<sup>1</sup>, Erwin Stolz<sup>2</sup>

<sup>1</sup>Department of Neurology, Jinling Hospital, Medical School of Nanjing University Nanjing 210002, China; <sup>2</sup>Neurological Practice, Department of Neurology, Justus-Liebig-University Giessen, Juergen-Ponto-Platz 2, Frankfurt am Main, Germany

*Contributions:* (I) Conception and design: R Liu; (II) Administrative support: R Liu; (III) Provision of study materials or patients: W Li; (IV) Collection and assembly of data: R Liu; (V) Data analysis and interpretation: R Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

\*On behalf of AME cerebrovascular Disease Cooperative Group

*Correspondence to:* Dr. Rui Liu. Department of Neurology, Jinling Hospital, Medical School of Nanjing University, 305# East Zhongshan Road, Nanjing 210002, China. Email: liurui8616@163.com.

**Abstract:** Occlusion of large arteries, such as terminal parts of internal carotid artery (ICA) and main stem of middle cerebral artery (MCA), often result in poor outcomes of the acute ischemic stroke (AIS) patients. Recently, randomized controlled trials (RCTs) have consistently confirmed the benefit of endovascular treatment in AIS patients. With the positive results of these studies, endovascular recanalization therapy has been recommended as standard stroke care by stroke guidelines. In this review, we describe the strategies of endovascular treatment, analyze the reasons of the superiority of the thrombectomy in recent trails. The therapeutic time window, better patient selection, expediting and enhancing recanalization, and the addition of neuroprotective agents are the important factors we should focus on in the future.

**Keywords:** Acute ischemic stroke (AIS); endovascular treatment

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## Endovascular treatment for the acute ischemic stroke (AIS): the past and the future

As one of the main causes of death and disability worldwide, AIS needs to be treated as quickly as possible in order for any causal treatment to be effective (1). Occlusion of large arteries, such as the terminal parts of the internal carotid artery (ICA) and the main stem of the middle cerebral artery (MCA), often result in poor outcomes of the AIS patients (2). Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has evolved to the standard treatment of AIS within the 4.5 hours' time window after symptom onset (3). Treatment beyond 4.5 hours is not backed by controlled studies. Even with intravenous thrombolysis the death rate of AIS is still up to 25%, leaving 50% patients with permanent disability (4).

Clear limitations of intravenous thrombolysis are the

short therapeutic window ( $\leq 4.5$  hours), haemorrhagic complications, and the overall recanalization rate. In clinical practice it is difficult to judge the thrombus volume, but easy to evaluate the site of occlusion. While MCA branch occlusions show a recanalization rate of approximately 60% six hours after stroke onset, MCA mainstem occlusions have a chance below 30% to fully recanalize within 6 hours (5). For increasing revascularization rates in large artery occlusions and to improve outcome other therapies such as endovascular treatment need to be explored.

## The strategies of endovascular treatment

### *Intra-arterial (IA) thrombolysis*

For AIS patients with large artery occlusion, IA thrombolysis can be used to improve the efficiency of drug

delivery into the thrombus. With the aim of recanalizing the occlusion, the microcatheter is placed at the proximal end of the occlusion and a high dose of fibrinolytic agent is released in close proximity of the thrombus (6). IA thrombolysis requires comparably smaller drug dosages to achieve recanalization than i.v. thrombolysis and the technical of intervention is considered simple. Although the technique is regarded technically simple it is more time-consuming than mechanical thrombectomy. In very proximal occlusion, recanalization rates are reported modest (7). But in more distal occlusions, such as M2 branches, the recanalization rates are higher. After IA thrombolysis, brain hemorrhagic and distal emboli are the common complications (8).

Prototype study for this approach is the pro-urokinase in acute cerebral thromboembolism (PROACT) II trial (9). However, pro-urokinase never has been clinically available, so that the study has a proof-of-principle character.

IA thrombolysis has never been approved by the US Food and Drug Administration (FDA) but is still frequently used around the world for emergency treatment of patients with ICA, MCA or basilar artery occlusion. During the intervention, researchers find that IA thrombolysis often fails to improve the outcome of patients, because large thrombi usually required a long time to be dissolved (10).

### Endovascular ultrasound-enhanced thrombolysis

The use of direct intravascular ultrasound for clot lysis was first described in 1974 in an animal model (11). The energies for endovascular ultrasound vary between 0.2–2.0 W/cm<sup>2</sup>, and the frequencies between 20 KHz to 2 MHz. Ultrasound can promote microstreaming, which is the motion of fluid around the thrombus (12). Ultrasound generates pressure waves, which increase the permeation of rt-PA into the fibrin network. Ultrasound energy enhances the binding of rt-PA to the fibrin within a matrix, and weakens the fibrin cross-links at the same time (12). Ultrasound transducers also can be incorporated into the catheters for IA delivery of the thrombolytic drug. The IA ultrasound device can emit a power of 400 mW to enhance the effect of thrombolytic drugs, which has been tested in the phase II–III of interventional management of stroke (IMS) trials (13).

### Endovascular angioplasty and stenting

Balloon angioplasty and stenting in cerebral artery occlusion is a technique that is similar to the approach taken in acute

myocardial infarction. Cerebral blood vessels are more prone to dissection because they are without firm muscular support. In the cerebral vessels, the approach to the occlusion position is often tortuous making navigation more difficult. To remove the obstacles of endovascular angioplasty and stenting in AIS patients, many catheters and devices designed for the cerebral artery have been developed in recent years.

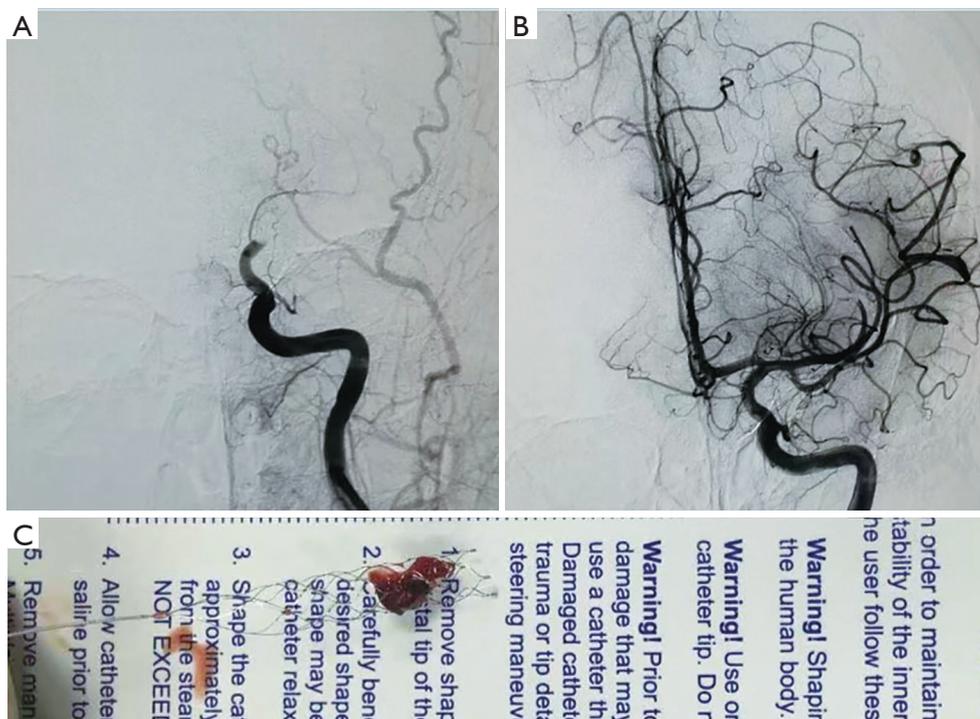
In a retrospective analysis of 19 patients, permanent stent afforded 79% successful recanalization. Due to the small sample, there were no cases of symptomatic intracranial hemorrhage (sICH) in the study (14). The results showed that stent-assisted recanalization is associated with a high recanalization rate. However, disadvantage of permanent stenting, such as the administration of dual antiplatelet therapy, is significant. The loading dose of clopidogrel can increase the risk of symptomatic ICH after the recanalization. At present, the use of permanent stents to the treatment of patients with cerebral artery occlusion has been restricted with the advent of embolectomy techniques.

### Thrombectomy techniques

Compared with pharmacologic thrombolysis, thrombectomy techniques have many advantages, including higher rates of recanalization and low risk of ICH. Thrombectomy techniques can currently be classified into 4 groups depending on the device used: the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) Retriever, the Penumbra System, the Solitaire FR revascularization device and TREVO Pro retriever (15).

The MERCi devices received FDA approval in 2004, which are deployed into the thrombus and works as a cork screw like retrieval tool (16). To achieve flow arrest and prevent distal embolization, the balloon of the guiding catheter is inflated proximal to the clot. After the removal of the clot, the proximal balloon is deflated and the circulation is restored.

The penumbra stroke system was approved by the FDA in 2007, which uses an aspiration catheter along with a separator to debulk and remove the thrombus (17). Stent-based mechanical thrombectomy such as solitaire FR Revascularization Device is a new concept in AIS treatment. With the self-expanding stents partially deployed, clot enmeshed into the stent, and the vessel is gently aspirated. Based on results from the Solitaire with the Intention for Thrombectomy (SWIFT) trial, the solitaire stent has been extensively used in Europe since 2010, and received FDA approval in March 2012 (18) (*Figure 1*). As same type device,



**Figure 1** Cerebral angiography before and after thrombectomy in patients with MCA occlusion (A) showing occlusion of the proximal MCA; (B) final angiogram post procedure; (C) showing recanalization of the vessel with clot captured in the Solitaire stent. MCA, middle cerebral artery.

TREVO Pro Stent Retriever mechanical embolectomy device approved by the FDA in August 2012, based on the results of the TREVO 2 trial (19).

### Important published studies about the endovascular treatment

#### *Pro-urokinase in acute cerebral thromboembolism (PROACT) II*

To confirm the safety and efficacy of IA thrombolysis in AIS patients caused by MCA occlusion, Prolyse in Acute Cerebral Thromboembolism (PROACT) II was designed (20). Patients in the group treated with IA pro-urokinase plus heparin within 3 to 6 hours from stroke onset get a higher 90 days good outcome rate compared with the group treated with heparin alone (40% vs. 25%). The rates of complete recanalization, defined as Thrombolysis in Myocardial Infarction (TIMI) grade 3, was 19% in the pro-urokinase plus heparin group, and only 4% in the heparin alone group. But the rate of sICH was 10% in the treated patients, and which was just 2% in the controls.

The mortality rates in the two groups have no significant difference (25% vs. 27%) (9).

#### *The IMS studies I and II*

The IMS I and II were designed to examine the effects of an initially lower dose of IV rt-PA (0.6 mg/kg) followed by IA rt-PA or/and IA ultrasound when recanalization was not achieved (18). The rates of recanalization (TIMI 2 to 3) were 56% in IMS-I and 60% in IMS-II. About 46% of IMS-II patients reached a mRS score of 0 to 2 at 3 months after stroke. In both studies, the mortality at the 3 months was 16%, and sICH rates were 6.3% and 9.9% respectively (21).

In the IMS trials, the method of reduced-dose IV rt-PA followed by endovascular therapy was used as a bridging concept. A large proportion of patients undergoing thrombectomy had i.v. rt-PA (0.9 mg/kg) prior catheter according the results of ECASS III 3.0–4.5 h after onset of stroke (22). The previous observational studies also supported the full dose IV rt-PA used, because the risks of sICH are acceptable (23).

### **MERCI study and Multi-MERCI study**

The MERCI study explored the safety and efficacy of the MERCI device in 151 patients. Patients enrolled in this study had both anterior and posterior circulation strokes. All the patients had large artery occlusions, and were treated within 8 hours of stroke onset (24). The results showed that the rates of recanalization to TIMI 2 to 3 in the MERCI study connected with a significant improvement was achieved in 46%. At 1 month after stroke, 22.6% of patients reached a mRS score  $\leq 2$ , and 34.1% of patients a NIHSS score improvement  $\geq 10$  points. At 3 months after stroke, the rate of mRS  $\leq 2$  improved to 27.7%, and NIHSS improvement  $\geq 10$  points to 32.4% respectively. The mortality lay at 43.5% at 90 days, and sICH was observed in 11 of 141 (7.8%) (24).

In the Multi-MERCI study, IV or IA rt-PA, mechanical clot disruption, and other adjunctive therapies were allowed prior using the MECRI device. Some of the patients were treated with the newer generation L5 device (25). All the 160 patients were treated within 8 hours of stroke onset, and 29% of the participants received IV rt-PA without recanalization before the procedure. The results showed that vessel recanalization was achieved in 55% of patients with the retriever alone, and improved to 68% when adjunctive therapies were used. Compared with in ICA and M1-MCA occlusions, the recanalization rates were higher in the posterior circulation (88% and 80% respectively). At 1 month, mRS  $\leq 2$  was achieved in 36% and NIHSS  $\geq 10$  improved to 26% of participants. Nine point eight percent of the participant suffered sICH, and the mortality was 34% at 90 days. Results showed that treatment with IV rt-PA before MERCI device deployment did not increase the risk of sICH. Multivariate analysis showed that recanalization was related to good outcome. Older age and higher admission NIHSS score were associated with mortality and poorer functional outcome.

### **SWIFT trial**

The participants of the SWIFT trial were all AIS patients. All patients received treatment with the Solitaire (n=58) or MERCI device (n=55) within 8 hours of symptom onset. Compared with the MERCI group, the recanalization (TIMI 2 to 3) rate in the Solitaire group was higher (83% *vs.* 48%), and the rate of favorable outcome (mRS  $\leq 2$ ) at 90 days was significantly increased. The mortality from any causes by 90 days in the Solitaire group was 9%, and which was 12% in the MERCI group (26).

### **Negative trials**

IMS-III was a placebo controlled trial evaluating endovascular intervention as a rescue therapy in patients who failed to improve after a reduced-dose IV rt-PA (0.6 mg/kg) thrombolysis within 3 hours of stroke symptom onset. Many endovascular therapy methods including IA rt-PA, EKOS catheter, MERCI devices, and the Penumbra system were used in the study. However, stent retrievers were only rarely employed. The planned study size was 900 participants but the trial was prematurely halted because of futility after 656 patients. The results showed that good functional outcome (mRS  $\leq 2$ ) at 90 days did not differ between the two groups. Rates of mortality and sICH were similar between the groups (27).

In the SYNTHESIS Expansion trial patients with AIS were included within 4.5 hours after symptom onset. Both the endovascular therapy group and the IV rt-PA group enrolled 181 patients each. The median time to initiation of therapy was 1 hour longer in the endovascular arm. Only 56 patients were treated with device, and only 18 patients were treated with a stent retriever. The results showed that good functional outcome (mRS  $\leq 2$ ) rates were not different between the groups in the intention-to-treat analysis after adjustment for age and stroke severity (42.0% *vs.* 46.4%). Adverse events of the two groups, including sICH, did not differ significantly (28).

Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) was a trial assessing the value of endovascular therapy using the MERCI device or the Penumbra device and IA rt-PA when necessary within 8 hours of stroke symptom onset in relation to whether patients had ischemic penumbra as defined by MR diffusion-perfusion mismatch. On final review, 58% of the 118 patients had a favorable penumbral pattern. The results showed that although patients with penumbra had smaller final stroke volumes, the overall rates of favorable outcome were low even among the patients with penumbra on MRI. Recanalization rates with endovascular therapy group were 67% among the participants with favorable penumbral pattern and 77% in those without penumbra (29,30).

Delayed time to treatment, inclusion of patients without artery occlusion or with distal occlusion, less effective devices used are common causes of the lack of benefit from embolectomy in these trials

### **Recent trials showed benefit of thrombectomy**

From 2015, five new trials showing the superiority of

endovascular treatment were published. The trials had a similar design and inclusion criteria: the therapeutic window for the endovascular treatment was 6 hours, proximal intracranial occlusion in the anterior circulation were required.

EXTEND-IA is the smallest trial demonstrating benefit of thrombectomy over intravenous thrombolysis with inclusion of only 70 patients who were within 4.5 hours of symptom onset and had confirmed internal carotid or MCA occlusion (31). The participants were randomized to two groups: IV rt-PA only and additionally thrombectomy with the Solitaire FR stent retriever. The primary outcomes of the trial were reperfusion at 24 hours and a reduction of the NIHSS score  $>8$  points within 3 days. Compared with the control group, the rates of reperfusion at 24 hours was higher in the endovascular treatment group (100% *vs.* 37%,  $P<0.001$ ), and the rate of early neurological improvement was higher (80% *vs.* 37%,  $P=0.002$ ). At 30 days outcome was better in the thrombectomy arm (mRS  $\leq 2$ ; 71% *vs.* 40%;  $P=0.001$ ). The mortality and sICH rates did not differ at 90 days (32).

The multicenter randomized clinical trial of endovascular treatment in the Netherlands (MR CLEAN) was a large trial with 500 patients from 16 different centers. Patients with anterior circulation large artery occlusion were randomly allocated to endovascular treatment plus usual care or usual care only. The use of intravenous rt-PA was not required in the usual care group, but 89% of the total sample received intravenous rt-PA before randomization. The primary outcome of MR CLEAN was a measure of functional independence (mRS  $\leq 2$ ) 90 days after the intervention. The results showed an absolute difference of 13.5 percentage points [95% confidence interval (CI), 5.9 to 21.2] in the rate of functional independence (mRS  $\geq 2$ ) in favor of the intervention (32.6% *vs.* 19.1%).

ESCAPE was a trial with 316 patients from 22 centers from the USA, Canada, South Korea, Ireland and the UK. The patients were randomized into standard care or standard care plus endovascular treatment. Unlike the other trials, the participants' treatment window was up to 12 hours after the stroke onset. The rate of functional independence at 1 month was significantly higher in the interventional group (53% *vs.* 29.3%,  $P<0.001$ ). The mortality rate in the endovascular thrombectomy group was reduced, while the rates of sICH were not significantly different. However, the rate of new ischemic strokes in other vascular territories was higher in the intervention group (33).

Because of the significant efficacy, the SWIFT PRIME trial was terminated early in 2014. From 2012 to 2104, 196

participants from 39 centers were randomized to IV rt-PA alone or to additional endovascular treatment. The Solitaire FR or Solitaire 2 devices were used in the endovascular treatment group. The primary outcome was functional independence (mRS  $\leq 2$ ) at 3 months. The rate of functional independence was much higher in the endovascular treatment group compared with controls (60% *vs.* 35%,  $P<0.001$ ). Mortality and sICH rates at 90 days were similar in the two groups (34).

The RESVASCAT trial was halted prematurely when positive results from other RCTs had been published. Two hundred and six eligible patients were enrolled. The participants include no recanalization after 30 minutes of the onset of IV rt-PA or ineligible IV rt-PA ineligible. The enrolled patients were randomized to endovascular treatment or medical therapy alone. Solitaire stent retriever was used in the study. Rates of functional independence (mRS  $\leq 2$ ) were higher in the endovascular treatment arm (43.7% *vs.* 28.3%). The safety variables did not differ between the two groups (35) (*Tables 1,2*).

The five recently trials published from 2014 have shown a superiority of interventional treatment plus IV rt-PA over IV rt-PA alone. The therapeutic windows are wider in the recent trials: 3 of them within 6 hours of symptom onset, 1 within 8 hours, and 1 within 12 hours. Beside the therapeutic window, the devices used, patients inclusion criteria were all important reasons of the superiority of the endovascular treatment (36).

In the three initial trials, one of the main limitations was the fact that first generation devices were used. Recent trials suggest that the recently developed stent retriever i.e., Solitaire FR are more effective than the first generation devices. The recanalization rates were improved and the time to achieve recanalization was shortened with stent retrievers. The results of the recently published positive trials reflect the superiority of these new devices.

The inclusion criteria of the trials are believed to greatly influence the positive results. Cases with proven proximal artery occlusion are less prone to respond to IV-rtPA and are associated with more voluminous thrombi. Eligible patients had an occlusion of the ICA, MCA or anterior cerebral artery (ACA).

Recent systematic review and meta-analysis of recent trials yielded a risk ratio of 1.56 (95% CI, 1.38 to 1.75) for good functional outcomes and 0.86 (95% CI, 0.69 to 1.06) for mortality, without heterogeneity among the results of the studies. Moderate to high quality evidence suggests that for patients with anterior circulation ischaemic stroke, bridge

**Table 1** Published important RCTs comparing endovascular thrombectomy with other interventions for AIS

Study name	Country	Recruitment onset and end	Device used	Sample size	Groups	Therapeutic window	Culprit artery	Primary outcome (90 days mRS)
Trials showed no benefit of thrombectomy								
IMS III	USA, Canada, Australia, Europe	2006.8–2012.7	MERC1 retriever, Penumbra system or Solitaire FR or endovasc t-PA	656	Endovascular Thrombectomy + IV rt-PA vs. IV rtPA	rt-PA was given within 3 hrs of symptom onset; randomisation done 40 minutes after rt-PA infusion onset	ICA, M1 and BA	Proportion with a mRS $\leq$ 2: 40.8% and 38.7% (95% CI, -6.1 to 9.1)
MR RESCUE	USA	2004.5–2011	MERC1 retriever, Penumbra' system	118	Endovascular Thrombectomy vs. best medical care	$\leq$ 8 hrs from stroke onset	ICA, M1 and M2	Mean score on the mRS: 3.9 vs. 3.9, P=0.99
SYNTHESIS EXP	Italy	2008.2–2012.4	Not specified	362	Endovascular therapies vs. IV rtPA	$\leq$ 6 hrs from stroke onset	Not specified	Proportion with a mRS $<$ 2: 30.4% and 34.8% (95% CI, -14.1 to 5.2)
Trials showed benefit of thrombectomy								
EXTEND- IA	Australia and New Zealand	2012.8–2014.10	Solitaire FR	70	Endovascular Thrombectomy + IV rt-PA vs. IV rt-PA	$\leq$ 6 hrs from stroke onset	ICA, M1, M2	mRS 71% vs. 40% Generalized OR =2.0; 95% CI, 1.2–3.8
MR CLEAN	Netherlands	2010.12–2014.3	Devices approved by the FDA or CE and approved by their steering committee	500	Endovascular therapies* vs. IV rt-PA	$\leq$ 6 hrs from stroke onset	ICA, M1, M2, A1 and A2	Proportion with a mRS $\leq$ 2: 13.5% (95% CI, 5.9–21.2)
ESCAPE	Canada, USA, South Korea, Ireland, UK	2013.2–2014.10	Use of retrievable Stents were recommended	316	Endovascular Thrombectomy+ IV rt-PA vs. IV rtPA	$\leq$ 12 hrs from stroke onset	ICA, M1, M1-MCA (2 or more M2-MCAs)	Proportion with a mRS $\leq$ 2: 53% and 29.3%; RR, 1.4; (95% CI, 1.4–2.4); OR, 2.6; (95% CI, 1.7–3.8)
SWIFT PRIME	USA/Europe	2012.11–2015.1	Solitaire FR or Solitaire 2	196	Endovascular Thrombectomy vs. IV rt-PA	$\leq$ 6 hrs from stroke onset	ICA, M1	Proportion with a mRS $\leq$ 2: 60% and 35%; RR =1.70; (95% CI, 1.23–2.33)
REVASCAT	Spain	2012.2–2014–12	Solitaire	206	Endovascular Thrombectomy vs. best medical care**	$\leq$ 8 hrs from stroke onset	ICA, M1	Proportion with a mRS $\leq$ 2: 43.7% and 28.2%; OR =2.1 (95% CI, 1.2–4.0)

\*, intra-arterial t-PA, mechanical thrombectomy or a combination of both; \*\*, standard care (including IV rt-PA). IV rt-PA, intravenous recombinant tissue-type plasminogen activator; ICA, internal carotid artery; MCA, middle cerebral artery; M1, segment 1 middle cerebral artery; M2, segment 2 middle cerebral artery; A1, segment 1 anterior cerebral artery; A2, segment 2 anterior cerebral artery; RCTs, randomized controlled trials; AIS, acute ischemic stroke.

**Table 2** Safety Measures of the published RCTs comparing endovascular thrombectomy with other interventions for AIS

Study	Country	Mortality	sICH
IMS III	USA, Canada, Australia, Europe	At 90 days 19.1% vs. 21.6% (P=0.52)	After rt-PA initiation 6.2% vs. 5.9% (P=0.83)
MR RESCUE	USA	At 90 days 18.7% vs. 24.1%	At 90 days 5% vs. 3.7% (P=0.24)
SYNTHESIS EXP	Italy	At day 7, 8% vs. 6% (P=0.53)	At day 7 6% vs. 6% (P=0.99)
EXTEND-IA	Australia and New Zealand	At 90 days 9% vs. 20% (P=0.18)	0% vs. 6% (P=0.49)
MR CLEAN	Netherlands	At 30 days 18.9% vs. 18.4%	At 90 days 7.7% vs. 6.4%
ESCAPE	Canada, USA, South Korea, Ireland, UK	At 30 days 10.4% vs. 19%	At 30 days 3.6% vs. 2.7%
SWIFT PRIME	USA/Europe	At 90 days 9% vs. 12% (P=0.50)	At 27 hrs 0% vs. 3% (P=0.12)
REVASCAT	Spain	At 90 days 18% vs. 15.5% (P=0.60)	At 90 days 1.9% vs. 1.9% (P=1.00)

treatment provides beneficial functional outcomes, without increased detrimental effects within 6 to 8 hours (37).

### What next?

At present, some RCTs are still recruiting or planned. The details of these studies are summarized in *Table 3*. Most frequent comparison is between endovascular thrombectomy plus IV rt-PA with IV rt-PA alone.

At present, the sample size of the studies about the thrombectomy is relatively modest. In the real world, whether intravascular therapy can benefit more stroke patients remains a problem. In many areas, IV rtPA is the preferred method for treatment of acute stroke due to the lack of endovascular treatment techniques. With the continuous improvement of diagnostic neuroradiology services, more and more patients can benefit from the IV rtPA. In the future, the model can also be used for the implementation of endovascular therapy.

To maximise the benefit and minimise the harm and costs of treatment, it is important to identify the patients who are most likely to respond to endovascular treatment. To achieve this goal, clinicians have to make decisions about the suitability of endovascular thrombectomy using patients clinical and image information. Researchers developed multivariable prediction models that combine baseline risks and clinical and imaging features to estimate the effect of treatment. The models performed moderately well to estimate the benefit of endovascular treatment in individual patients. When the patients complete the imaging examination and begin the standard IV rt-PA treatment, the doctor and the family can use the calculator online to decide whether to

further the endovascular treatment. This model also can help AIS patients and their families making decisions at a critical time. More studies are needed to incorporate findings from imaging studies into the model and compare the effect of these models with clinical results (38).

The penumbra is defined as reversible ischemia can be saved with successful reperfusion. With successful recanalization, the patients can be differentiated into reversible and viable ischemia up to 12 hours after onset according pretreatment perfusion imaging. However, most studies derived the imaging-based identification of penumbra from untreated patients. As such, advanced penumbral imaging was not considered with a major effect on treatment outcomes. Future penumbral imaging that derived from patients who have undergone prompt reperfusion may provide endovascular treatment opportunity that is not determined only by the time window (39).

At present, the favorable results for endovascular treatment were achieved at the background of IV t-PA. When no significant clinical response of IV rt-PA was observed, the patients were enrolled in the endovascular treatment group. But such nonresponse does not mean that the IV rt-PA complete futility, because IV t-PA could enhance subsequent endovascular treatment by platelet aggregation through the way of fibrinolysis and inhibition of shear stress. Even if IV rt-PA is not effective in all patients, such therapy may have supporting effects on endovascular treatment. Moreover, in the subgroups of the patients who received previous IV rt-PA and those who did not, recanalization degree and procedure duration might be different (40). Future trials of endovascular treatment might lead to a renewed appreciation of IV rt-PA or confirm the

**Table 3** Description of ongoing RCTs comparing endovascular thrombectomy with other interventions for AIS

Study	Country	Intervention groups	Device type brand	Sample size	Therapeutic window	Culprit artery	Recruitment onset/end	Current status
PISTE	United Kingdom	Endovasc. Thrombectomy + IV rt-PA vs. IV rt-PA	Not specified mechanical thrombectomy	800	≤5.5 hrs	ICA, M1, M2	2012.12–2017.8	This study is currently recruiting participants
BASICS	Italy, Netherlands, Switzerland	Endovasc. Thrombectomy + IV rt-PA vs. IV rt-PA	MERCI Trevo, Penumbra, Solitaire	750	≤6 hrs	Basilar artery	2011.10–2017.10	This study is currently recruiting participants
POSITIVE	USA	Endovascular Thrombectomy vs. best medical care	Penumbra, Solitaire and TREVO	750	≤12 hrs	ICA, M1	2013.9–2016.5	This study is currently recruiting participants
DAWN	USA	Endovascular Thrombectomy vs. best medical care	Trevo	500	6 to 24 hrs	ICA, M1	2014.6–2017.7	This study is currently recruiting participants
RESILIENT	Brazil	Endovascular Thrombectomy vs. best medical care	Solitaire FR	690	≤7.5 hrs	ICA, M1	2015.3–2018.3	Not yet recruiting
WASSABI	USA	Endovascular thrombectomy vs. IV rt-PA vs. Standard medical care*	Merci Penumbra	90	Unknown time of onset but less than 24 hours since last seen normal	MCA	2011.11–2014.2	Status unknown
BEST	China	Endovascular treatment + standard medical therapy vs. standard medical* therapy alone	Solitaire FR, Trevo	344	≤8 hrs	Basilar artery	2015.4–2018.3	This study is currently recruiting participants

\*, standard of care in acute ischemic stroke including intravenous thrombolysis. AIS, acute ischemic stroke; IV r-tPA, intravenous recombinant tissue-type plasminogen activator; ICA, internal carotid artery; MCA, middle cerebral artery; M1, segment 1 middle cerebral artery; M2, segment 2 middle cerebral artery; RCTs, randomized controlled trials.

exactly effect of endovascular treatment in suitable patients.

Anesthesia used during endovascular treatment is also an important question in need to be answered. In recent trials, general anesthesia was used only in a small part of the participants. It is unknown whether the patients with general anesthesia had differences in outcome as compared with the patients with local anesthesia. A recent meta-analysis and systematic review found outcomes among AIS patients who had undergone general anesthesia was poorer than among those who had undergone conscious sedation and local anesthesia (41). The rate of respiratory complications was increased and the rate of good functional outcome was decreased in the general anesthesia group. The procedure

time between the two groups did not differ. However, this question has not been definitely answered yet.

In recent trails, participants enrolled in the studies often had high stroke severity. Patients with severe stroke may be more likely to reach improved functional outcome. But in the real world, many patients with low stroke severity also need to be treated with appropriate methods. More characterization of the patients enrolled in future trials is needed to determine who will benefit from endovascular therapy.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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