

Perspective

Advances in endovascular therapy for ischemic cerebrovascular diseases

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Abstract

Endovascular therapy for ischemic cerebrovascular diseases has developed rapidly in recent years. The latest clinical trials of acute ischemic stroke have shown promising results with the continued advancement of concepts, techniques, and materials. Mechanical thrombectomy is recommended in the treatment of acute ischemic stroke caused by large vessel occlusion of the anterior circulation, according to the guidelines updated in Europe, USA, and China. The long-term therapeutic efficacy of endovascular stenting for carotid artery stenosis has also been proved noninferior to that of carotid endarterectomy. However, the latest clinical trials have shown that the efficacy of stenting for intracranial artery and vertebral artery stenosis is inferior to that of medical treatment alone, which needs urgent attention through further development and studies.

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Introduction

Ischemic cerebrovascular disease is among the leading causes of morbidity and mortality in the world that not only cause physical and emotional pain in the patients but also inflict a great financial burden on their families and the society. Endovascular treatment of

ischemic cerebrovascular diseases has progressed greatly in recent years. The efficacy of mechanical thrombectomy for acute ischemic stroke (AIS) caused by intracranial large vessel occlusions has been proved superior to that of medical treatment alone. The former is considered a milestone in the development of interventional therapy for ischemic cerebrovascular diseases and is now recommended in most treatment guidelines. Additionally, the long-term efficacy of stenting for symptomatic carotid stenosis has been proved noninferior to that of carotid endarterectomy. However, the latest clinical trials of endovascular stenting of intracranial artery and vertebral artery stenoses have not yet yielded positive results, and sufficient evidence of their efficacy is still lacking. Here, the authors outline the major advances in

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interventional therapy for ischemic cerebrovascular diseases in addition to some urgent issues raised in recent years.

Endovascular therapy of AIS

Endovascular therapy of AIS has undoubtedly achieved a landmark progress in 2015. The results of five new randomized controlled trials (RCTs), such as the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN), have been reported, which indicate that mechanical thrombectomy is significantly superior to intravenous thrombolysis (IVT) in patients with AIS.^{1–5} Compared to the three previous RCTs, such as the IMS (Interventional Management of Stroke) III trial that obtained negative results, the positive results of the five new RCTs reported in 2015 were probably owing to the following factors: (1) large artery occlusions of the anterior circulation that were confirmed by computed tomography angiography (CTA) or magnetic resonance angiography; (2) the use of newer generation of thrombectomy devices, including the stent retriever, thrombus aspiration device, etc., that have a significantly improved ability to retrieve the thrombus with a significantly lesser time required to obtain successful recanalization; and (3) the exclusion of patients with large infarct volume. A meta-analysis of the three RCTs published in 2013 and the five subsequent RCTs showed that compared to medical treatment, mechanical thrombectomy was associated with a higher revascularization rate in patients with AIS and did not increase the risk of symptomatic intracranial hemorrhage or all-cause mortality rates at 90 days.⁶ Therefore, several European and American professional associations and societies have published or updated the consensus and guidelines, which now clearly recommend mechanical thrombectomy (level of evidence I) for all patients with AIS caused by large artery occlusions of the anterior circulation who meet the indications. Although IVT is still needed, the interventional therapy should be performed as soon as possible (level of evidence I). It is not necessary and also not recommended to monitor the response of patients to IVT before the administration of interventional therapy.^{7,8} On the other hand, the Chinese Society of Neurology (CSN) of the Chinese Medical Association (CMA) and the Chinese Stroke Association also published guidelines that recommend mechanical thrombectomy as the interventional therapy in patients with AIS caused by large artery occlusions of the

anterior circulation within 6 hours of the onset of symptoms.^{9,10} Recently, studies that reported the five RCTs in 2015 further include a meta-analysis of the pooled data from these studies. The results showed that interventional embolectomy therapy is effective in most patients with AIS caused by proximal occlusion of large arteries in the anterior circulation, regardless of their age, the severity of preprocedural stroke, and whether they have undergone IVT.¹¹ Based on the above findings, it is expected that the treatment of AIS is about to be revolutionized.

Certainly, numerous issues related to interventional therapy in AIS remain controversial, as current studies have inconsistent findings and lack a thematic approach. For example, there is still a lack of consensus on whether imaging is needed to guide the selection of patients with AIS who are eligible for interventional thrombectomy, whether to select the widely applied and rapid CT scans for Alberta Stroke Program Early CT (ASPECT) score or multiphase CTA, or to select CT perfusion and/or MRI that are more sensitive but relatively time-consuming.¹² Besides, these studies differently suggest whether IVT must be administered in primary-care hospitals before the patients are transferred to comprehensive stroke centers capable of conducting interventional therapy, or if the patients should directly be transferred to superior hospitals for an earlier interventional therapy. While some studies suggest that bridging IVT is beneficial to patients who undergo interventional thrombectomy,¹³ other studies show that bridging thrombolysis is not an independent predictor of favorable clinical outcomes, and there is no significant difference in the complication rates between patients with and without bridging thrombolysis.¹⁴ In addition, several issues need to be addressed, such as the choice of local anesthesia or general anesthesia during the surgery, the choice of stent thrombectomy or aspiration thrombectomy or a combination of the two methods, and whether patients with acute large artery occlusions of the posterior circulation or those beyond the recommended time window can also benefit from endovascular therapy.

Endovascular therapy of extracranial carotid stenosis

For symptomatic extracranial carotid stenosis, high-risk surgical patients have been proven to benefit from the carotid artery stenting (CAS); however, whether CAS or carotid endarterectomy (CEA) is more suitable for non-high-risk surgical patients is still unknown.

The International Carotid Stenting Study (ICSS) in Europe is an RCT that include the largest number of cases; the long-term follow-up results reported in 2015 suggest that there is no significant difference in the long-term functional outcome and the risks of fatal or disabling stroke and restenosis between patients who underwent CAS and those who underwent CEA.¹⁵ In 2016, another RCT called Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) carried out in USA and Canada also reported results of over 10 years of follow-up, which indicated that there was no significant difference in the incidences of periprocedural stroke, myocardial infarction or death, and postprocedural recurrent ipsilateral stroke between patients in the CAS and CEA groups.¹⁶

However, evidence is still lacking on whether to administer standard medical therapy, CAS, or CEA for asymptomatic extracranial carotid stenosis. Asymptomatic Carotid Trial (ACT) I is an RCT that compare the efficacy of CAS and CEA in non-high-risk surgical patients with asymptomatic carotid stenosis. The results showed that CAS is noninferior to CEA in its incidence of composite endpoints after 1 year post-surgery. However, there was no significant difference in the rates of non-procedure-related stroke, all strokes, and survival, between the two groups.¹⁷ The recent Asymptomatic Carotid Surgery Trial-2 (ACST-2) is an RCT that includes the highest number of cases at present, to directly compare the efficacies of CAS and CEA. Its interim results showed that the 30-day mortality and major morbidity in patients with asymptomatic carotid stenosis were only 1% after surgical treatments (CAS or CEA), although the findings regarding the comparison of CAS and CEA were not reported.¹⁸ In addition, there are three other RCTs currently being conducted in Europe and USA, and are still recruiting patients to directly compare the efficacies of CAS/CEA and medical therapy in asymptomatic carotid stenosis and indirectly compare the efficacies of CEA and CAS.

Endovascular therapy of intracranial artery stenosis

For intracranial artery stenosis, the extended follow-up results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial showed that the efficacy of medical treatment alone is still superior to that of stenting.¹⁹ Meanwhile, another RCT called VISSIT (Vitesse Intracranial Stent Study for Ischemic Therapy) that compared the efficacy of

stenting and medical treatment, has also been terminated in advance. In contrast to the Wingspan self-expanding stent used by the SAMMPRIS trial, the VISSIT study used the Vitesse balloon-expandable stent; however, its results published in 2015 were inadequate: the 30-day all-cause mortality and 1-year stroke or transient cerebral ischemic attack rate in patients of the stent group were significantly higher than those in patients of the medical group. Obviously, the relatively low success rate of stenting in the study has influenced the representativeness and persuasiveness of its results to a certain extent.²⁰ Despite these disappointing outcomes, another post-marketing surveillance study, Wingspan Stent System Postmarket Surveillance Study (WEAVE), has promising preliminary results that showed that the periprocedural complication rates of the Wingspan stent in the treatment of intracranial artery stenosis was only 4.4% under a narrowed indication.²¹ Simultaneously, the results of a multicenter registry study in China also showed that the primary endpoint event rate (stroke, transient ischemic attack, or death) within 30 days of stenting in patients with severe symptomatic intracranial atherosclerotic stenosis with poor collateral compensation was only 4.3%.²² In another prospective multicenter registry study conducted in China, the incidence of stroke or mortality rate at 30 days following intracranial stent placement were only 2%.²³ Currently, there is another important prospective multicenter RCT, China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS), which is still recruiting patients to compare the efficacies of stenting and medical treatment in intracranial severe stenosis.²⁴ Since the SAMMPRIS trial mainly focused on Western populations while intracranial artery stenosis has an especially high incidence among Eastern populations, the results of the CASSISS study are noteworthy. Therefore, we believe that the selection of patients who may benefit from the interventional therapy for intracranial artery stenosis should be studied in future.

However, since stenting has a higher complication rate, some physicians attempted to improve the current technique through the use of the balloon alone to perform a submaximal or undersized inflation, or the use of the balloon in combination with the closed-cell Enterprise stent (beyond indication). The preliminary results indicate that it is associated with lower periprocedural complications, in-stent restenosis, and recurrent stroke rates during short-term follow-up.^{25,26} Its efficacy still requires confirmation through further large-scale controlled studies.

Endovascular therapy of vertebral artery stenosis

The number of patients subjected to stenting for the treatment of symptomatic vertebral artery stenosis has gradually increased in recent years; however, thematic studies determining whether it has superior efficacy to that of medical therapy are still very rare. Vertebral Artery Stenting Trial (VAST) is an RCT that has currently recruited the highest number of patients to compare stenting and medical treatment for symptomatic vertebral artery stenosis; its results indicate that stenting is not better than medical treatment with respect to the periprocedural complication rate and the 3-year incidence of recurrent vertebrobasilar stroke.²⁷ It should be noted that all the periprocedural stroke complications in the stent group of this study occurred in patients with intracranial vertebral artery stenosis. Another recent meta-analysis that compare the efficacies of medical treatment and interventional therapy in patients with intracranial vertebrobasilar stenosis, also performed a subgroup analysis that only included patients with intracranial vertebral artery stenosis; the results indicate that the interventional therapy is probably more advantageous.²⁸ In addition, since some recent studies have shown that patients with symptomatic intracranial vertebral artery stenosis have a higher risk of posterior circulation ischemia than patients with extracranial vertebral artery stenosis, we believe that future clinical trials will focus on interventional therapy for patients with symptomatic intracranial vertebral artery stenosis.

References

- Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11–20.
- Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372:1009–1018.
- Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* 2015;372:1019–1030.
- Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* 2015;372:2285–2295.
- Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372:2296–2306.
- Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA.* 2015;314:1832–1843.
- Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO, Karolinska stroke update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke.* 2016;11:134–147.
- Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2015;46:3020–3035.
- Chinese Stroke Association. Chinese guide to endovascular therapy for acute ischemic stroke 2015 [in Chinese]. *Chin J Stroke.* 2015;07:590–606.
- Chinese Society of Neurology. Early interventional endovascular treatment of acute ischemic stroke in China [in Chinese]. *Chin J Neurol.* 2015;05:356–361.
- Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731.
- Menon BK, Campbell BC, Levi C, et al. Role of imaging in current acute ischemic stroke workflow for endovascular therapy. *Stroke.* 2015;46:1453–1461.
- Guedin P, Larcher A, Decroix JP, et al. Prior IV thrombolysis facilitates mechanical thrombectomy in acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2015;24:952–957.
- Weber R, Nordmeyer H, Hadisurya J, et al. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. *J Neurointerv Surg.* 2016. <http://dx.doi.org/10.1136/neurintsurg-2015-012236>. pii: neurintsurg-2015-012236.
- Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet.* 2015;385:529–538.
- Brott TG, Howard G, Roubin GS. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med.* 2016;374:1021–1031.
- Rosenfield K, Matsumura JS, Chaturvedi S. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med.* 2016;374:1011–1020.
- ACST-2 Collaborative Group, Halliday A, Bulbulia R, et al. Status update and interim results from the asymptomatic carotid surgery trial-2 (ACST-2). *Eur J Vasc Endovasc Surg.* 2013;46:510–518.
- Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet.* 2014;383:333–341.
- Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA.* 2015;313:1240–1248.
- Alexander M, Zauner A, Chaloupka J, et al. O-016 interim report on the weave™ intracranial stent trial: 50 consecutive patients. *J Neurointerv Surg.* 2015;7:A9.
- Liao ZR, Zhang Y, Shuai J, et al. Peri-operative registry of symptomatic intracranial arterial stenosis in China: a multicenter study. *J Stroke Interv.* 2015;1:143–158.
- Gao P, Wang D, Zhao Z, et al. Multicenter prospective trial of stent placement in patients with symptomatic high-grade intracranial stenosis. *AJNR Am J Neuroradiol.* 2016;37:1275–1280.
- Gao P, Zhao Z, Wang D, et al. China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): a new,

- prospective, multicenter, randomized controlled trial in China. *Interv Neuroradiol.* 2015;21:196–204.
25. Dumont TM, Sonig A, Mokin M, et al. Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective Phase I study. *J Neurosurg.* 2016;125:964–971.
 26. Lee KY, Chen DY, Hsu HL, et al. Undersized angioplasty and stenting of symptomatic intracranial tight stenosis with enterprise: evaluation of clinical and vascular outcome. *Interv Neuroradiol.* 2016;22:187–195.
 27. Compter A, van der Worp HB, Schonewille WJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. *Lancet Neurol.* 2015;14:606–614.
 28. Abuzinadah AR, Alanazy MH, Almekhlafi MA. Stroke recurrence rates among patients with symptomatic intracranial vertebrobasilar stenoses: systematic review and meta-analysis. *J Neurointerv Surg.* 2016;8:112–116.

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