



## Review Article

# Mechanical thrombectomy for acute ischemic stroke with occlusion of the M2 segment of the middle cerebral artery: A literature review

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**J Cerebrovasc Endovasc Neurosurg.**  
**2021 September;23(3):193-200**

Received: 9 November 2020

Revised: 2 February 2021

Accepted: 21 February 2021

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Thanks to new generation devices, mechanical thrombectomy (MT) has substantially evolved and become the standard treatment for patients with acute occlusion of the internal carotid artery or proximal middle cerebral artery (MCA) (M1 segment). However, the role and benefit of MT in patients with distal MCA (M2 segment) occlusion remain unclear. Therefore, there is a need for further studies. To evaluate the efficacy and safety of MT for M2 occlusion, this article reviews the natural course of M2 occlusion, the evidence regarding MT for M2 segment occlusion, clinical outcomes of MT for M2 occlusion, and treatment outcomes according to device type.

**Keywords** Intervention, Middle cerebral artery, Stroke, Thrombectomy

## INTRODUCTION

Mechanical thrombectomy (MT) using new generation devices has substantially evolved. Five randomized controlled trials (RCTs) published in 2015 reported the benefits of MT over standard medical treatment in patients with acute ischemic stroke (AIS) caused by emergent large vessel occlusion (ELVO) of the anterior circulation.<sup>1)3)10)13)29)</sup> The positive data provided by these RCTs initiated a worldwide groundbreaking change in AIS therapy. Consequently, MT has become the standard treatment modality for patients with AIS and ELVO who meet the relevant criteria. The American Heart Association (AHA)/American Stroke Association (ASA) strongly recommends that patients with AIS receive endovascular MT when the causative occlusion is located in the internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1), in addition to other criteria (Class I; Level of Evidence A).<sup>20)</sup>

However, although these previous trials yielded large data, the role of MT in patients with isolated MCA M2 segment occlusion remains unclear. Moreover, no

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randomized trials focused on the efficacy and safety of MT in patients with ELVO in the M2 segment. Therefore, current guidelines for stroke treatment suggest that patients with an M2 occlusion could be treated using endovascular treatment (EVT). However, the efficacy of MT for M2 occlusion remains unclear and further studies are required.

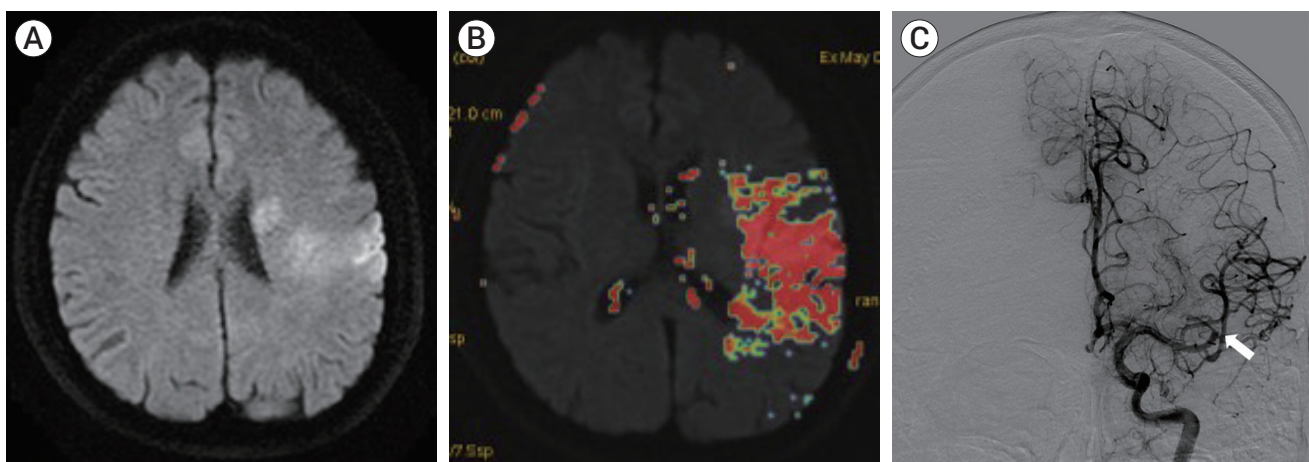
This study aimed to assess the safety and efficacy of MT for isolated M2 segment occlusions. Specifically, we reported the radiologic and clinical outcomes of MT for patients with isolated M2 segment occlusion by reviewing the recent literature with respect to the best medical treatment, comparison with M1 segment occlusion, and treatment outcomes according to device type (aspiration vs. stent-retriever) used for MT.

**Evidence regarding mechanical thrombectomy for isolated M2 segment occlusions**

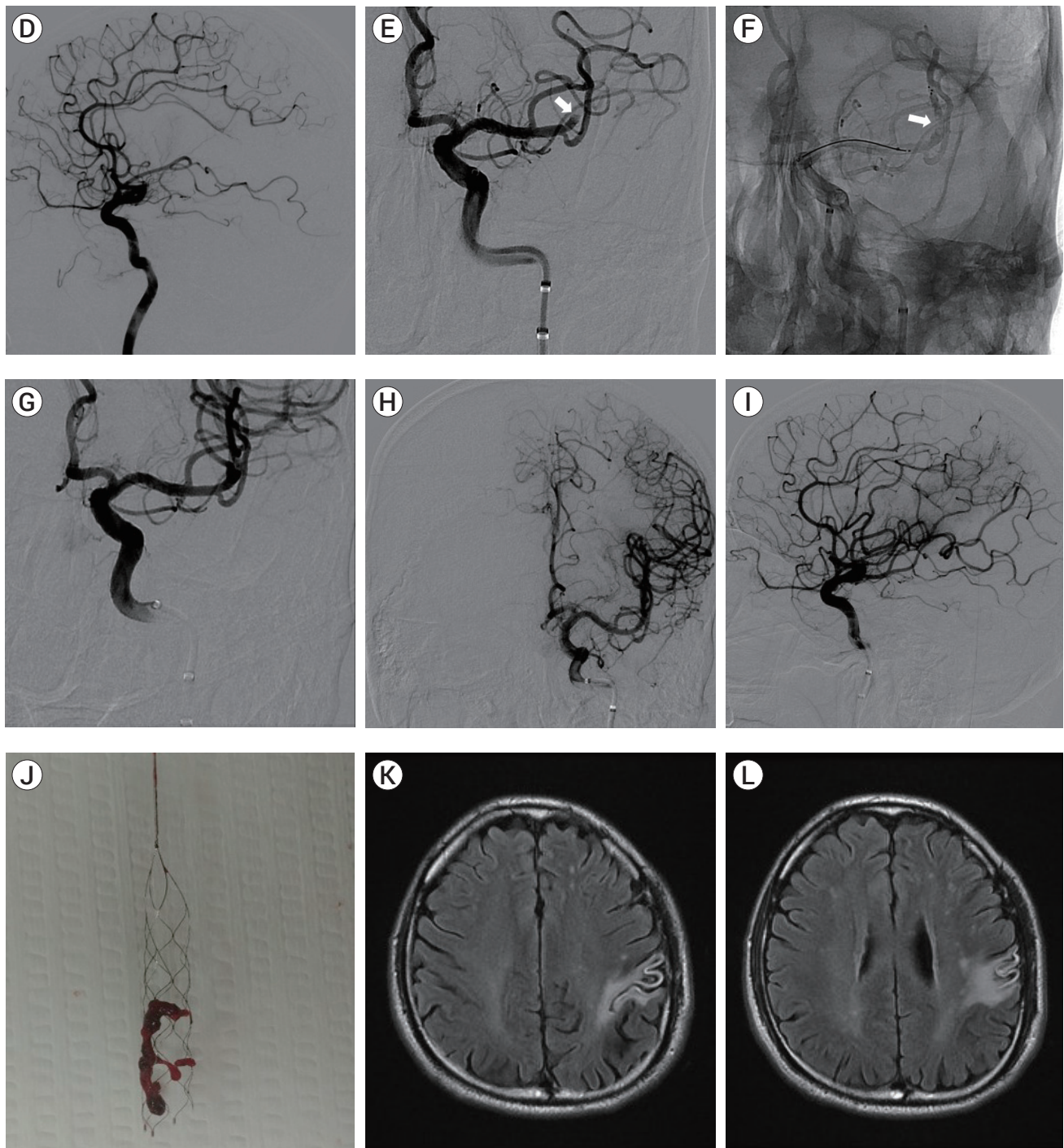
The clinical benefit of MT for M2 occlusion has been long controversial.<sup>19</sup> Given the limited evidence regarding the outcomes or safety of isolated M2 occlusions, well-defined recommendations are currently unavailable. Based on five recent randomized trials, MT is currently recommended as the standard treatment for patients with ELVO.<sup>13)10)13)29</sup> However, these previous trials mainly focused on AIS caused by occlusion of the distal ICA or M1 segment.<sup>20</sup> Among these trials, only MR CLEAN (7.8%) and EXTEND-IA (14%) explicitly included M2 segment occlusions while SWIFT PRIME,

REVASCAT, and ESCAPE excluded patients with isolated M2 occlusion. However, approximately 10% of patients included in the REVASCAT and SWIFT PRIME trials presented M2 occlusion despite this being an exclusion criteria, probably because most patients with M2 occlusions were misclassified as having M1 occlusion at trial enrollment.<sup>26</sup>

A subgroup meta-analysis of the five randomized trials on MT, which analyzed data from 94 patients with M2 occlusion of which 51 had undergone MT, reported no significant clinical benefit in the 90-day modified Rankin scale (mRS) scores after MT compared with the best medical treatment (odds ratio [OR] 1.28; 95% confidence interval [CI] 0.51-3.21).<sup>11</sup> However, these trials provided limited evidence for M2 occlusion treatment, since they partly assessed the benefit of MT in patients with M2 occlusion; further, the results could be underpowered given the small sample size extracted from the RCTs.<sup>11</sup> Although several retrospective studies have reported the poor natural history of M2 occlusion<sup>16</sup> and the acceptable clinical outcomes for MT of M2 occlusions using second-generation devices,<sup>2)4)6)28</sup> there is a need for RCTs on MT for M2 occlusion to determine the safety and effectiveness of EVT compared with the best medical therapy. However, this may not be feasible in real clinical settings since MT is routinely performed in patients with M2 occlusion in numerous institutions based on the evidence yielded by few RCTs on patients with M2 occlusion (Fig. 1).<sup>26</sup> AHA-ASA currently



(Continue on next page Fig. 1)



**Fig. 1.** Illustrative case of mechanical thrombectomy for a patient with M2 occlusion. (A, B) DWI on admission shows acute infarction in the pre- and postcentral gyrus with perfusion defect in the left MCA territory. (C, D) Initial cerebral angiography reveals M2 segment occlusion of the left middle cerebral artery (anteroposterior and lateral views). (C) White arrow indicates the occlusion site. (D) The superior branch of MCA is not shown due to the occlusion. (E, F) Mechanical thrombectomy is performed using a stent-retriever. (E) White arrow indicates the occlusion site. (F) Recanalized blood flow and thrombus (white arrow) are identified after stent deploy. (G) The occlusion is recanalized after the first pass. (H, I) Final cerebral angiography (anteroposterior and lateral view) shows successful recanalization (mTICI 3). (J) Stent-retriever (Solitaire stent) and retrieved clot. (K, L) Magnetic resonance FLAIR images acquired at 1-postoperative week show no infarction extension compared with the initial diffusion-weighted image. DWI, Diffusion-weighted imaging; MCA, middle cerebral artery; mTICI, modified thrombolysis in cerebral ischemia, FLAIR, fluid-attenuated inversion recovery.

recommends that MT may be a reasonable treatment option for selected patients with M2 occlusion (Class IIb; Level of Evidence B-R).<sup>20)</sup>

### Natural course of M2 occlusion

M2 occlusions comprise approximately 20-41% of anterior circulation strokes and limited data exist regarding the natural course of untreated M2 occlusion. Only 44% of patients with M2 occlusion achieve successful recanalization after receiving intravenous tissue plasminogen activator (IV tPA), which leads to several patients having poor outcomes compared to those with M1 occlusion.<sup>24)27)</sup>

Two studies have investigated the natural course of M2 occlusion.<sup>12)16)</sup> Lima et al. assessed the rate and predictors of long-term outcomes in patients with acute ICA, M1, and M2 occlusion who did not receive any reperfusion treatment.<sup>16)</sup> Among 126 patients, 48 (38.1%) patients had M2 segment occlusion with 22 (45.8%) of them having a baseline National Institute of Health Stroke Scale (NIHSS) score of  $\geq 10$ . The rate of favorable outcome (6-month mRS score 0-2) in the overall group was 38.5% (10 of 26), 38.5% (20 of 52), and 54.2% (26 of 48) among patients with ICA, M1, and M2 occlusion, respectively. However, a higher baseline NIHSS score (NIHSS $\geq 10$ ) was an important independent factor for poor outcomes in the logistic regression model. Notably, the proximal occlusion site (ICA vs. M1 vs. M2) was not independently associated with outcomes.<sup>16)</sup> Moreover, even patients with more distal occlusion had lower NIHSS scores, which was not statistically significant, and this is because of variations in the degree of collateral flow, at least partly. Therefore, the pleomorphic clinical presentation of stroke may occur regardless of the intracranial arterial occlusion level; further, a significant proportion of these patients could be potential candidates for reperfusion trials.<sup>16)</sup>

Another study on the natural course of M2 occlusion reported that the absence of reperfusion therapy for M2 occlusion caused poor outcome.<sup>12)</sup> Moreover, a study reported that patients with M2 segment occlusion initially presented with small-sized infarction area, which

resulted in a significantly wider infarction area.<sup>30)</sup> These studies suggested that non-treated M2 occlusion could develop massive ischemic stroke causing death or moderate-to-severe disability at discharge.

A population-based study by Rai et al.<sup>25)</sup> used 3-year data on tertiary level hospital discharge and regional country. Isolated M2 occlusion was reported in approximately 4% of all patients with AIS, which comprised the second most common occlusion site following M1 occlusion (8.5%). Clinical outcome data indicated that the median NIHSS score of M2 occlusion was 12 (inter quartile range 5-18). Further, favorable outcomes, poor outcomes, and death were observed in 43%, 57% and, 27% of patients excluded from endovascular therapy (only treated with IV tPA), respectively. They reported an NIHSS score of 9 as the optimal cutoff point to predict poor outcomes (sensitivity, 85.7%; specificity, 67.4%), and concluded that M2 occlusion could lead to the development of serious neurological deficits, as well as significant morbidity and mortality. Therefore, there is a need to expand the AIS category amenable to MT; specifically, patients with isolated M2 occlusion presenting higher baseline deficit (NIHSS  $\geq 9$ ).<sup>25)</sup>

### Best medical treatment vs. MT

There have been few direct comparisons of the MT efficacy with the best medical treatment in patients with M2 occlusions. As mentioned above, a subgroup meta-analysis of five RCTs reported no significant clinical benefit of MT compared with the best medical treatment; however, due to their small sample size the result was underpowered.<sup>11)</sup> Furthermore, performing an RCT comparing MT with the best medical treatment may present ethical problems in a real clinical setting.

Competing issues highlight the uncertainty of the treatment method for M2 segment occlusions. Some disagreements regarding MT for M2 segment occlusions result from the procedural safety of MT in small-caliber vessels, as well as the evidence supporting the concept that more distal occlusions have a better response to intravenous thrombolysis.<sup>5)</sup> Contrastingly, other physicians have concerns regarding the lower reperfusion rate

of medical treatment, including intravenous thrombolysis, compared to that of MT for large vessel occlusions, which could cause large infarct volume with severe neurologic deficits. Regarding the comparison of EVT with intravenous thrombolysis for isolated M2 segment of MCA occlusion in AIS, a post-hoc analysis based on the Interventional Management of Stroke III trial reported that randomized patients who received EVT had lower 3- and 12-month mortality; further, they had lower grades of disability. However, there were non-significant higher odds (OR: 2.7; 95% CI: 0.6.13.6;  $p=0.22$ ) for achieving excellent functional outcome. This analysis demonstrated the benefit of EVT for isolated M2 occlusion but did not show statistical significance. Further, this study had a small sample size (51 patients) and very limited use of stent retrievers.<sup>23)</sup>

A multicenter retrospective cohort study by Sarraj et al.<sup>28)</sup> pooled patients with AIS and ELVO isolated to the M2 segment from 10 US academic centers. They included 522 patients and divided them into two groups based on treatment as follows: endovascular treatment (288 patients) and medical management groups (234 patients). There was a significantly higher rate of good clinical outcomes in patients who underwent MT compared with those who received medical treatment (62.8% vs. 35.4%). Even patients treated with medical management had a higher rate of IV tPA and an earlier hospital arrival than patients who underwent MT. Multivariate analyses revealed that MT-treated patients showed three times the odds of favorable outcomes (OR, 3.2; 95% CI, 2-5.2;  $p<0.001$ ). However, there was no significant between-group difference in symptomatic intracerebral hemorrhage (5.6 % vs. 2.1 % for the EVT group vs. the medical management group;  $p=0.10$ ). Although this study had the inherent limitations of the retrospective design and selection bias, including patients considered likely to benefit from EVT in the EVT group, their results support the benefit of EVT over medical treatment alone. Moreover, the lack of a between-group difference in symptomatic hemorrhage supports EVT safety for M2 segment occlusions.<sup>28)</sup>

Menon et al.<sup>17)</sup> analyzed patients with M2 segment

occlusion from the HERMES Collaboration of seven RCTs (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, THRACE, EXTENDED-IA, and PISTE). They found that MT for patients with M2 segment occlusion presented improvement in 90-day functional independence compared with the best medical treatment. They included 130 patients (endovascular treatment group [n=67] vs. control group [n=63]) and observed a successful recanalization rate (modified thrombolysis in cerebral ischemia score 2b or 3) in 59.2% of patients in the endovascular treatment group. Functional independence was observed in 58.2% and 39.7% of patients in the endovascular treatment and control groups, respectively. They reported that the treatment effect favored the endovascular treatment group over the control group (adjusted OR 2.39, 95% CI 1.08 to 5.28,  $p=0.03$ ) for a 90-day mRS score of 0-2. Moreover, there was no statistical difference in complications, including post-procedural symptomatic intracerebral hemorrhage or major procedural complications. Further, there was a maximal treatment effect favoring EVT when the involved M2 segment was the dominant branch (n=73, adjusted OR 4.08, 95% CI 1.08 to 15.48,  $p=0.04$  for 90-day mRS score of 0-2, 61.5% EVT vs. 44.1% control). However, there was no significant difference in the treatment effect with respect to the type of M2 segment occlusion. These results require cautious interpretation since differences in baseline characteristics could potentially explain the better outcomes in the EVT group, even though there was no statistical difference in heterogeneity. Furthermore, selection bias may have influenced the results. Nonetheless, this analysis is based on high-quality data from seven randomized trials and provides important evidence supporting the EVT efficacy for patients with MCA occlusion in the M2 segment.<sup>17)</sup>

### MCA-M1 vs. MCA-M2 thrombectomy outcome

Several recent studies have reported the benefit of MT for MCA-M2 segment occlusion. Additionally, several studies have demonstrated acceptable clinical and radiological outcomes for MT treatment for M2 segment occlusion using modern second-generation MT devices.<sup>2)4)6)7)14)22)</sup>

However, MT of the MCA-M2 segment tends to be more technically challenging because of its smaller caliber and more vessel tortuosity compared to the MCA-M1 segment. MT devices are designed to be suitable for the proximal artery segment and are less suitable for the arterial profile with access demand of the distal arterial segment. To this point, some physicians have expressed concern regarding procedural complications arising from the small caliber and the tortuous MCA-M2 segment course. Moreover, individual differences in the branching pattern of the M2 segment could increase the risk of procedural complications.

A recent systematic review and meta-analysis conducted by Saber et al. investigated the clinical and radiologic outcomes of MCA-M2 occlusion thrombectomy using modern second-generation devices, including stent retriever and penumbra aspiration system, and compared the results with those of MCA-M1 occlusions.<sup>26)</sup> Twelve studies with 1080 patients with M2 thrombectomy were included; among them, six studies with 1712 patients (M1 occlusion [n=1375], M2 occlusion [n=337]) were analyzed to compare M1 and M2 occlusion thrombectomy results. Regarding baseline characteristics, initial NIHSS scores were relatively lower in patients with M2 occlusion compared with those with M1 occlusions (13.5 vs. 16.7). However, there were no significant differences, as well as heterogeneity in other factors, including the time of onset to recanalization, number of passes, and IV tPA usage. Regarding clinical outcomes, the proportion of patients with functional independence (mRS score 0-2) was significantly higher in patients with M2 occlusion (OR 1.46, 95% CI 1.15 to 1.86; p=0.002; I<sup>2</sup>=20%). Furthermore, regarding radiologic outcomes, there was no significant difference (M2 occlusion [84.9%] vs. M1 occlusion [84.2%]) in the successful recanalization rate (OR 1.05, 95% CI 0.77 to 1.42; p=0.78; I<sup>2</sup>=18%) with no significant across-study heterogeneity. However, the symptomatic ICH rate was higher in patients with M2 occlusion (15%) than in those with M1 occlusion (4.7%). This meta-analysis showed comparable MT results between patients with M2 and M1 occlusions despite the higher post-procedural symptomatic ICH rates. These

results highlight the favorable outcomes associated with MT, particularly in patients with M2 occlusion.<sup>26)</sup>

Regarding procedural complications, Mönch et al.<sup>18)</sup> reported associations between occluded vessel diameters and outcomes. They analyzed 168 and 98 patients with M1 and M2 occlusions, respectively, who underwent MT and focused on the relevance of the arterial diameter on the occlusion site and outcomes. Regarding the highest cerebrovascular spatial resolution, the vessel diameter was measured using digital subtraction angiography. The diameter at the occlusion site and NIHSS score at admission were significantly higher in patients with M1 occlusion. Contrastingly, there were no significant between-group differences in the rate of procedure-related complications and post-procedural hemorrhage, as well as in clinical outcomes. There was a positive correlation of vessel site with admission NIHSS score but no correlation between the vessel diameter and 3-month mRS score. Finally, neither the segment nor the diameter of the occluded vessel correlated with the rate of successful recanalization and intracranial hemorrhage, as well as good clinical outcomes, in MT-treated patients with AIS.<sup>18)</sup>

Most recently, two retrospective multicenter studies compared the MT efficacy for M1 and M2 segment occlusions. Their results were similar to previous findings of comparable outcome and safety profile of MT for M2 and M1 segment occlusion.<sup>8)19)</sup>

### Stent-retriever versus aspiration in M2 thrombectomy

Direct aspiration thrombectomy using a distal access catheter is an effective and safe EVT strategy for AIS with ELVO. Recent updated guidelines show that direct aspiration thrombectomy as first-line MT is comparable to stent retriever thrombectomy (Class I; Level of Evidence A).<sup>21)</sup> However, in most retrospective studies addressing distal intracranial artery occlusions, stent retriever thrombectomy was mainly used for target vessel recanalization.<sup>4)6)15)28)</sup>

A recent meta-analysis by Saber et al. compared MT of M2 occlusion using a stent retriever with local

aspiration. Successful recanalization rate (TICI 2b/3) was observed in 87% and 80% of patients treated with stent retriever and local aspiration, respectively; moreover, favorable functional outcomes were observed in 57.6% and 46.6% of patients treated with stent-retriever and local aspiration, respectively. There was no significant difference in successful recanalization and functional outcome according to device type. Further, there was no significant across-study heterogeneity.<sup>26)</sup> The ASTER randomized trial (contact aspiration versus stent retriever for successful revascularization) reported no significant differences in reperfusion and clinical outcomes between contact aspiration and stent retriever as first-line strategies for isolated M2 occlusions.<sup>9)</sup>

## CONCLUSIONS

Our literature review shows that despite the weak evidence for M2 occlusion compared to that for M1 occlusion, MT for patients with isolated M2 occlusion can be safely performed, and that the clinical outcomes of MT for M2 occlusion are comparable to those of guideline-based MT for M1 occlusion. There is a need for future multicenter cohort studies to evaluate factors associated with favorable outcomes in MT of distal intracranial artery occlusions.

## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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