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Mechanical Thrombectomy for All LVO – Is It Feasible? – Recent Evidence to Expand the Current Stroke Guidelines

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Abstract

Mechanical thrombectomy (MT) has established its role as a standard care of acute ischemic stroke due to large vessel occlusion (LVO). Current early stroke management guidelines have defined certain selection criteria for LVO patients undergoing MT to achieve the most benefit. However, it is still uncertain if some other LVO patients who do not meet these criteria can also benefit from MT. In this review, we research the latest evidence on efficacy and safety of MT for LVO in various unique stroke populations, such as advanced age, pre-stroke disability, LVO with minor stroke, large infarct volume, poor mismatch profile, very late time window, posterior circulation LVO and distal medium-sized vessel occlusions. By comparing the benefits and risks of MT with best medical management only, we may develop further subgroup-specific criteria to expand our capacity to best treat these unique LVO populations.

Keywords: Acute ischemic stroke, Cerebral ischemia, Mechanical thrombectomy, Endovascular treatment, Large vessel occlusion

Introduction

Stroke is a leading cause of death and disability worldwide. In recent decades, advances in acute ischemic stroke (AIS) treatment have greatly improved patient outcomes, especially in patients with large vessel occlusion (LVO). Mechanical thrombectomy (MT) with or without thrombolysis has shaped the landscape for management of acute LVO stroke, particularly with recent time window expansion and patient selection based on perfusion imaging. However, not all LVO patients are eligible for these treatments according to the current guidelines, and some may still have poor prognosis despite revascularization. Recent studies have challenged the guidelines and suggested that some patients who were previously considered poor candidates for MT may still benefit from this procedure. Here we will review the current evidence and discuss the management of LVO stroke beyond the guideline recommendations.

Factors Currently Determining Candidacy for MT

MT has established its role as a first-line treatment of AIS with LVO. The 2019 stroke guideline recommended the following class 1A criteria for patients within 6 hours of onset to undergo MT: (1) pre-stroke modified Rankin Scale (mRS) 0-1; (2) causative occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) segment 1 (M1); (3) age >=18 years; (4) NIH Stroke Scale (NIHSS) >=6; (5) Alberta Stroke Program Early CT Score (ASPECTS) >=6; and (6) groin puncture within 6 hours of symptom onset [1]. Beyond these criteria, the benefits are uncertain although MT may still be reasonable. For those AIS patients presented in an extended time window (within 6 to 16 hours of onset) who have LVO in the anterior circulation and meet DAWN or DEFUSE-3 eligibility criteria, MT is also recommended [1]. However, a recent Swiss study included 190 patients with anterior circulation LVO in the extended time window who did not meet the DEFUSE-3 or DAWN inclusion

criteria [2]. Among these non-DEFUSE-non-DAWN patients, 54% received MT, and patients in the MT group had higher odds of favorable outcomes at 90 days (mRS shift towards lower categories, OR 1.46 [95% CI, 1.02 to 2.10]) without increased rates of symptomatic intracranial hemorrhage (sICH) (5% vs. 2%, p=0.63) when compared with the best medical management (BMM) alone group [2]. This study calls for more permissive inclusion criteria for patients with LVO to undergo MT. Thrombectomy ineligible stroke subpopulations are being actively studied in ongoing clinical trials. In the next sections, we will discuss recent new developments for individual criteria involved in patient selection for MT that may expand the patient candidacy for MT.

Age

The current guideline supports MT in elderly patients (**Table 1**). In a meta-analysis of 5 randomized controlled trials (RCTs) (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) for LVO within 6-8 hours of onset using stent retrievers, there was favorable 90-day mRS with MT over BMM alone across patient age subgroups, including ≥ 70 years of age [3]. The pooled patient-level data from these RCTs also showed that MT had a favorable effect over BMM in patients ≥80 years of age [4,5]. A recent meta-analysis from 7 RCTs demonstrated that among 77 patients ≥ 85 years old, a positive benefit of MT was observed over control group on outcome measures [6]. Similarly, in the extended window MT trials, DAWN showed better functional outcome of MT over BMM alone in patient ≥ 80 years old with favorable imaging and clinical profiles [7]. Of note, DAWN patients above 80 years of age had a more stringent inclusion criterion than younger patients to ensure smaller ischemic cores and lower NIHSS. DEFUSE-3 also demonstrated benefits of MT over BMM for patients ≥70 years

Table 1. Summary of outcomes in LVO patients with advanced age undergoing MT

reference	author(s)	study type	sample size	patient subgroup	time after stroke onset	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
3	Bush *et al.*	meta-analysis		>=70	within 6-12 hours	MT vs. BMM	90-day mRS ordinal analysis		OR 2.26 (1.20–4.26)*	0.0113*
4	Goyal *et al.*	meta-analysis	198	>=80	within 6-12 hours	MT vs. BMM	90-day mRS ordinal analysis		cOR 3.68 (1.95-6.92)*	
5	Campbell *et al.*	meta-analysis	381	>=70	within 6-12 hours	MT vs. BMM	90-day mRS ordinal analysis		OR 3.16 (2.05-4.86)*	
			129	>=80					OR 3.46 (1.58-7.60)*	
6	McDonough *et al.*	meta-analysis	77	>=85	within 6-12 hours	MT vs. BMM	90-day mRS ordinal analysis		OR 4.20 (1.56-11.32)*	
7	Nogueira *et al.*	RCT	54	>=80	6-24 hours	MT vs. BMM	90-day utility weighted mRS		adjusted difference 2.3 (0.3-4.2)*	
8	Albers *et al.*	RCT	98	>=70 but < 90	6-16 hours	MT vs. BMM	90-day mRS 0-2		RR 3.91 (1.36-15.46)*	
10	Zhoa *et al.*	systemic review	3954	MT		>=80 vs. <80	90-day mRS 0-2	26.1% vs. 46.6%	OR 0.40 (0.32–0.50)*	<0.00001*
							90-day mortality	29.2% vs. 16.6%	OR 2.26 (1.73–2.95)*	<0.00001*
							sICH	7.4% vs. 6.3%	OR 1.28 (0.89–1.84)	0.18
							recanalization	66.3% vs. 68.1%	OR 0.72 (0.55–0.95)*	0.02*
11	Finitsis *et al.*	retrospective of rigistry data	1708	MT		80-90 vs. <80	90-day mRS 0-2	30.2% vs. 52.8%	OR 0.38 (0.28-0.51)*	< 0.001*
						>90 vs. <80		12.7% vs. 52.8%	OR 0.2 (0.09-0.45)*	< 0.001*
12	Friedman *et al.*	retrospective single center	347	MT		>90 vs.80-89 vs. <80	90-day mRS 0-2	15% vs. 13.54% vs. 40.2%		
							sICH	5% vs. 4% vs. 2.6%		
							90-day mortality	55% vs. 28% vs. 19.48%		0.03*
14	Rahangdale *et al.*	retrospective matched cohort	214	MT		>=90	90-day mortality	43.5% vs. 10.4%	OR 9.33 (2.88-47.97)*	<0.0001*
							sICH	13.0% vs. 3.0%	OR 6.00 (1.34-55.20)*	0.02*
16	Sussman *et al.*	retrospective single center	108	MT		90-99 vs. 80-89	90-day mRS 0-2	12.5% vs. 19.7%		0.54
							sICH	21.4% vs. 6.4%		0.03*

RCT: randomized controlled trial
* statistical significance

old with favorable imaging mismatch [8]. However, patients above 90 years of age were excluded from this trial.

Although MT for elderly patients is clinically feasible and more effective compared with conservative management, increased age was found to be associated with significantly poorer clinical outcomes [9] (**Table 1**). A systematic review from 3954 patients across 16 studies showed that older patients of 80 years or older undergoing MT had lower odds of functional independence and higher odds of mortality at 90 days than younger patients [10]. This study also found a trend toward higher rates of sICH, as well as significantly lower rates of recanalization in elderly patients. Another study from 1,708 patients in the ETIS registry in France showed the positive effect of MT diminished significantly with increasing age: compared to the 18-80 years of age group, the odds for achieving a good functional outcome at 90 days after the procedure decreased in the 80-90 and >90 years groups 11. Increasing age was also associated with increased mortality (**Table 1**). Multiple other retrospective studies in octogenarians and nonagenarians also support that patients with advanced age were unlikely to achieve functional independence and at higher odds of mortality and symptomatic ICH despite similar high rate of successful recanalization [12-16]. Compared with octogenarians, nonagenarians appear to have significantly worse outcomes [16].

To better select elderly patients who will likely benefit from intervention, many studies have investigated the predictors of good outcome in patients of age ≥ 80 undergoing MT. Lower pre-stroke mRS [17], lower admission NIHSS score [17-19], higher ASPECTS [18-20], smaller ischemic core on perfusion imaging [14,21] are independent predictors of good outcome. Post thrombectomy parameters including successful recanalization [17,19,20,22], smaller final infarct volume [23], and absence of sICH [17] are also considered strong predictors for better clinical outcome. Among all the predictors, successful recanalization seems to be the most influential [17,22].

Although higher mortality rates and less frequent favorable outcomes than younger patients, octogenarians and nonagenarians should not be deprived of MT. Like any other treatment decision in elderly patients, consideration of comorbidities and risks should always factor into the decision-making for MT. Future studies should focus on the patient selection algorithm and identify subgroups of elderly patients that could benefit the most from MT.

Pre-stroke Modified Rankin Scale (mRS)

Almost all major early or extended window LVO clinical trials have excluded patients with pre-stroke mRS >2 who exhibited higher rates of unfavorable clinical outcome and mortality after MT compared to those with previous no or mild disability (mRS 0-2) [24,25]. The current stroke guideline is uncertain about the benefits of MT in LVO patients with pre-stroke mRS >1 within 6 hours after onset and did not address MT in extended time window with existing disabilities [1].

An early study including 50 patients with mild baseline disability (mRS 0-1) and 46 with moderate disability (mRS 2-4) found that, if good outcome was re-defined to also include "return to baseline of function at 90 days" or "return of Rankin", there were no significant differences in good outcome between those with mild and moderate pre-stroke disability (43% vs. 24%, $p = 0.08$), although there was a trend of worse outcome in moderate disability patients [26]. Seker *et al.* also reported in 136 cases of pre-stroke mRS 3-4 (81.6% with mRS 3) with MT, 24.0% with mRS 4 achieved pre-stroke functional level compared with 20.7% of patients with mRS 3. The proportion of hospital mortality and mortality at 90 days was not statistically significant, but markedly higher in patients with premorbid mRS 4 [27].

Several larger observational studies also support this notion (**Table 2**). A study of 761 LVO patients with MT including one-third having moderate pre-stroke disability observed that 36.7% patients with pre-stroke mRS 0-1 vs. 26.7% of pre-stroke mRS 2-3 showed no worsening than their pre-stroke mRS. However, patients with pre-stroke disability were more likely to die by 90 days (14.3% vs 40.3%) [28]. Another study included 591 patients with 90 having pre-stroke mRS ≥3 showed that recanalization rates (80.0% vs 85.0%), sICH (2.2% vs 6.3%) and the proportion of patients returning to pre-stroke functional level (22.7% vs 14.8%) did not significantly differ between those mRS <3 and mRS ≥3. Patients with pre-stroke disability had higher complication rates during hospital stay (55.2% vs 40.1%, $p < 0.01$) and mortality at 3 months (48.9% vs 24.3%, $p < 0.001$) [29]. A recent study of 2,487 patients treated with MT including 409 patients with moderate pre-stroke disability (mRS 2-3) suggested that patients with mRS 2-3 had similar chance of return to baseline function (24% vs. 30%), although with higher risk of sICH and long-term mortality [30].

For severe pre-stroke disability with mRS 4-5, a retrospective study of 33 such patients reported procedural outcomes (84% successful recanalization and 6.2% rate of sICH) and rate of return to baseline function (36%) was comparable to that reported in the literature for patients with no pre-stroke disability, however, this needs to be interpreted carefully due to a limited sample size [31].

There are limited studies directly comparing MT with BMM alone in patients with pre-stroke disability (**Table 2**). Siegler *et al.* investigated 554 LVO patients with mRS 2-4 presenting in the extended time window (6-24 hours) and found that MT was associated with a higher probability of return of pre-stroke mRS by 90 days compared with BMM alone [32]. In another study, Sykora *et al.* studied effects of MT vs. BMM in LVO patients with pre-stroke mRS ≥3 using propensity score matching. 168 patients in each group were identified and it

Table 2. Summary of outcomes in LVO patients with pre-stroke disbility undergoing MT

reference	author(s)	study type	sample size	patient subgroup	time after stroke onset	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
26	Slawski *et al.*	retrospecitve	96	MT, age >=80		mRS 0-1 vs. 2-4	90-day mRS 0-2 or ROR	43% vs. 24%		0.08
27	Seker *et al.*	retrospecitve	136	MT		mRS 3 vs. 4	90-day ROR	20.7% vs. 24%		0.788
28	Salwi *et al*.	retrospecitve	761	MT		mRS 2-3 vs. 0-1	90-day mRS 0-1 or ROR	36.7% vs. 26.7%	aOR 0.90 (0.60-1.35)	0.6
							90-day mortality	14.3% vs 40.3%	aOR 2.83 (1.84, 4.37)*	<0.001*
29	Larsson *et al.*	retrospecitve	591	MT		mRS <3 vs. >=3	90-day ROR	22.7% vs 14.8%		0.062
							racanalization	80.0% vs 85.0%		0.211
							sICH	2.2% vs 6.3%		0.086
							complication	40.1% vs. 55.2%		<0.01*
							90-day mortality	24.3% vs. 48.9%		<0.001*
30	Millan *et al.*	retrospecitve	2487	MT		mRS 0-1 vs. 2-3	90-day ROR	24% vs. 30%	OR 0.79 (0.57-1.08)	0.149
							sICH	3% vs. 5%	OR 2.04 (1.11-3.72)*	0.02*
							90-day mortality	18% vs. 31%	OR 1.74 (1.27-2.39)*	0.001*
32	Siegler *et al.*	retrospecitve	554	mRS 2-4	6-24 hours	MT vs. BMM	90-day ROR		OR 3.10 (1.20-7.98)*	0.02*
33	Sykora *et al.*	retrospecitve with PSM	336	mRS >=3		MT vs. BMM	90-day ROR	28% vs. 19%	aOR 2.54 (1.16 to 5.57)*	0.02*
							24-48h NIHSS decrease >=8	29.8% vs. 10.7%	aOR 2.72 (1.26 to 5.92)*	0.01*
							90-day mortality	42.3% vs. 63.7%	aOR 0.27 (0.15 to 0.51)*	<0.001*
							sICH	4.2% vs. 2.4%		0.27
34	Tanaka *et al.*	retrospective	339	mRS 2-4		MT vs. BMM	90-day ROR	28% vs. 10.9%	aOR 3.01 (1.55-5.85)*	< 0.01*
							72h NIHSS decrease >=4		aOR 6.52 (2.23–19.08)*	<0.01*
							sICH	4.0% vs. 4.3%		1.00
							90-day mortality	17.7% vs. 26.8%	aOR 1.28 (0.48–3.38)	0.62

ROR: return of Rankin; PSM: propensity score matching

* statistical significance

showed MT was associated with higher odds of returning to baseline mRS at 3 months, early neurological improvement, and lower risk of 3-month mortality without increased risk of sICH [33]. A Japanese study of 339 LVO mRS 2-4 patients showed again MT was associated with higher odds of return to baseline function at 3 months than BMM (28.0 vs. 10.9%), and sICH rates were similar between the groups. However, the MT group was younger and had lower mRS [34].

Taken together, current studies have demonstrated comparable efficacy of MT in patients with pre-morbid disability as in those without, including similar rates of successful recanalization, sICH, and return to pre-stroke level of disability, although they have higher rate of mortality. In the absence of high-quality evidence, it has been recommended to pursue shared decision-making with patients or family members and being upfront about the uncertain evidence instead of excluding these patients from MT [35]. The decision to offer MT to this patient population should be made on a case-by-case basis, considering the patient's preferences, values, and goals of care. The nature of an individual patient's disability must also be considered, as different types of disabilities may predispose patients to different prognosis. For example, a patient with a mRS of 4 due to paraplegia from a remote trauma will likely have a better outcome than a patient with a lower mRS whose disability is due to advanced cancer. Favorable predictors associated with return of premorbid functional status, such as high ASPECTS and low NIHSS [27,30,32], may be utilized during the decision-making process.

LVO with Minor Stroke

The current guideline is uncertain about benefits of pursuing MT in LVO patients with NIHSS < 6 on presentation [1]. It is still controversial in terms of efficacy and safety for minor strokes

undergoing immediate MT.

Several studies raised concerns about worsening outcomes for minor strokes with MT (**Table 3**). In a retrospective study of LVO with NIHSS < 6, a total of 216 propensity score matched subjects was divided into tPA alone and MT ± tPA groups. The favorable outcome of mRS 0-1 at 90-day appeared similar between groups (63% vs. 65.7%), however, MT group was

Table 3. Summary of outcomes in LVO patients with minor stroke undergoing MT

reference	author(s)	study type	sample size	patient subgroup	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
36	Manno *et al.*	retrospective with PSM	216	NIHSS < 6	MT/tPA vs. tPA alone	90-day mRS 0-1	63% vs. 65.7%	OR 0.94 (0.51-1.72)	0.84
37	Wolman *et al.*	retrospective	47	NIHSS < 6	MT vs. BMM	90-day mRS0-2	56.3% vs. 64.7%		0.82
						sICH	11.8% vs. 3.3%		0.25
						length of hospital stay	7.6 ± 7.2 vs. 4.3 ± 3.9 days		0.04*
38	Sarraj *et al.*	pooled corhort	540	NIHSS < 6	MT vs. BMM	90-day mRS 0-2	77.4% vs. 75.6%	aOR 1.29 (0.82-2.03)	0.27
						neuro decline	19.6% vs. 6.7%		<0.001*
						sICH	16.3% vs. 1.3%		<0.001*
39	Schwarz *et al.*	retrospective with PSM	624	NIHSS < 6	MT/tPA vs. tPA alone	90-day mRS 0-1	68.8% vs. 78.9%	aOR 0.46 (0.30-0.72)*	0.001*
						90-day mRS 0-2	57.5% vs. 72.4%	aOR 0.52 (0.32-0.84)*	0.007*
						sICH	3.3% vs. 1.1%		0.082
40	Zhao *et al.*	systemic review and meta-analysis	2135	mild stroke patients with low NIHSS	MT vs. BMM	90-day mRS 0-2		OR 1.10 (0.74-1.64)	0.65
						90-day mRS 0-1		OR 1.03 (0.79-1.35)	0.8
						90-day mortality		OR1.80 (0.88-3.65)	0.11
						sICH		OR 3.21 (1.98-5.22)*	< 0.001*
41	Sarraj *et al.*	retrospective multicenter cohort study	214	NIHSS < 6	MT vs. BMM	90-day mRS 0-1	55.7% vs. 54.4%	aOR 1.3 (0.64-2.64)	0.47
						90-day mRS 0-2	63.3% vs. 67.8%	aOR 0.9 (0.43-1.88)	0.77
						sICH	5.8% vs. 0%		0.02*
42	Dargazanli *et al.*	retrospective multicenter cohort study	301	NIHSS < 8	MT vs. BMM (18% with rescue MT)	90-day mRS 0-1	65.9% vs. 62.6%	aOR 1.12 (0.65-1.93)	0.68
						90-day mRS 0-2	81.2% vs. 74.8%	aOR 1.33 (0.71-2.50)	0.38
						any ICH	16.5% vs. 6.1%	aOR 1.84 (0.76-4.47)	0.18
43	Nagel *et al.*	retrospective	300	NIHSS < 6	MT vs. BMM	90-day mRS 0-2	84.4% vs. 70.1%	aOR 3.1 (1.4-6.9)*	0.03*
44	Griessenauer *et al.*	systemic review and meta-analysis	413	NIHSS < 6	MT vs. BMM	90-day mRS 0-2		OR 9.27 (1.71-50.29)*	0.01*
45	Xiong *et al.*	meta-analysis	581	NIHSS < 8	MT vs. BMM	90-day mRS 0-2		OR 1.68 (1.08-2.61)*	
						90-day mortality		OR 0.64 (0.32-1.29)	
						sICH		OR 3.89 (1.83-8.27)*	

PSM: propensity score matching

* statistical significance

marginally inferior to tPA alone regarding outcome across all levels of disability and mortality [36]. A smaller case control study of 47 patients with minor stroke and LVO also demonstrated unfavorable risk-benefit of MT due to increased overall rate of longer hospital stay, less odds of discharge home, and ICH comparing with BMM [37]. Sarraj *et al.* reported from a pooled international cohort of 540 patients, functional independence (90-day mRS 0-2) was similar between MT and BMM groups, however, MT group had worse safety profile with significantly increased rates of neurological decline (19.6% vs 6.7%, $p < 0.001$) and sICH (16.3% vs 1.3%, $p < 0.001$) [38]. Schwarz *et al.* most recently analyzed 1037 patients with anterior circulation LVO and minor stroke (NIHSS<6) who were propensity score matched to MT + IV tPA vs. IV tPA alone (n=312 each group). MT + IV tPA was independently associated with worse functional outcomes at 3 months as well as higher rates of sICH, including hemorrhagic transformation and SAH [39].

Some studies suggested similar effects between MT and BMM in minor stroke patients with LVO (**Table 3**). A meta-analysis from 13 studies including 2135 patients showed similar clinical outcomes at 90 days in the two groups, although patients who underwent MT had higher risk of sICH [40]. A retrospective multicenter cohort study of 214 patients showed no difference in excellent and independent functional outcomes in minor strokes (NIHSS <6) receiving MT vs. BMM alone, but with increased sICH rates in MT group (5.8% vs. 0%, P=0.02) [41]. Another multicenter cohort study compared LVO patients with minor stroke (NIHSS <8) who underwent urgent MT with those had BMM but were allowed for rescue MT with neurological worsening. The MT group included 170 patients while the BMM group included 131 patients with 18% eventually receiving rescue MT. The functional (excellent and favorable) outcomes and safety endpoints (all-cause death and any ICH) were comparable between the two groups [42].

In contrast, many other studies supported the concept that MT is safer and more effective than BMM in LVO with minor stroke (**Table 3**). A retrospective analysis of 80 out of 300 patients undergoing MT favored MT for good outcome (mRS 0-2 at day 90) over BMM (84.4% vs. 70.1%however, no safety concerns were reported (sICH or 90-day mortality) [43]. An earlier meta-analysis compared subgroups of BMM only, IV tPA alone and MT, and found that in patients not eligible for IV tPA but underwent MT were more likely to experience good 90-day mRS than BMM. There was no significant difference in functional outcome between MT and IV tPA alone, and no reported sICH or death in both groups [44]. Another meta-analysis of a total of 581 LVO patients with NIHSS < 8 comparing MT with BMM alone showed a significant difference that the patients treated with MT were associated with improved 90-day mRS. There was no difference in 90-day mortality between the two groups. However, sICH occurred more frequently in the MT group [45]. In a retrospective analysis from two large databases, Hauseen *et al.* compared 88 patients with BMM alone and 30 with MT. MT was statistically associated with lower NIHSS at discharge (p=0.04), favorable NIHSS shift (p=0.03), and increased independence rates at discharge (p=0.03) as well as outpatient follow-up (p=0.04) [46]. In addition, from a health-economic standpoint, MT resulted in lifetime cost savings of $2821 (health care perspective) or $5378 (societal perspective) and an increment of 1.27 quality-adjusted life years compared with BMM alone, indicating dominance of additional EVT as a treatment strategy in patients with minor stroke [47].

Given the controversy of MT in patients with minor stroke with LVO, there is thus an urgent need for randomized clinical trials to define the effectiveness of MT in this patient population. However, before reaching that point, careful patient selection for MT is still the key for a better outcome. Saleem *et al.* reported among 122 LVO patients with NIHSS < 6, 19.7% had ≥ 4 points deterioration on NIHSS at a median of 3.6 hours (1-16) from arrival. 54% of those with declining NIHSS had rescue MT, and were more likely to be independent at discharge than those without rescue MT (73% vs 38%; P=0.02), although trending towards to a lower rate of independence at discharge than those patients without deterioration (50% vs. 70%, P=0.06) [48]. Similarly, another study showed 9 out of 22 medically treated LVO patients with minor stroke had subsequent deterioration requiring MT. Median time from arrival to deterioration was 5.2 hours (2-25). The rescue MT was still independently associated with a beneficial NIHSS shift (-4.2 [95% CI, -8.2 to -0.1], p=0.04) [49]. Therefore, it is essential to identify LVO patients with minor stroke who may have a high likelihood of early decline, in whom MT may be most beneficial.

Seners *et al.* developed and validated an ENDi score that is based on the vessel occlusion site and length of the thrombus [50]. The more proximal occlusion site and the longer thrombus, the higher the ENDi score, which indicates a higher odd of deterioration on NIHSS within the first 24 hours that cannot explained by ICH or another identified causes. ENDi probability was approximately 3%, 7%, 20%, and 35% for scores of 0, 1, 2 and 3- 4, respectively. It is reasonable to consider MT as the treatment strategy if ENDi score ≥ 2. Besides ENDi score, other potential positive predicators for better outcome have also been investigated over the years. It was found that MT plus IV tPA has less favorable outcome than IV tPA alone in patients with perfusion mismatch volume <40 ml; however, in mismatch >40 ml, there was no significant difference [51]. This is also supported by Sarraj *et al.* that MT was associated with improved functional independence with target mismatch [38]. On the other hand, Wang *et al.* found that patients with poor outcomes, when compared with those with good outcomes, had a much larger perfusion lesion volume (median 80 mL vs 41 mL, $p < 0.001$). A perfusion lesion of 65 mL was the optimal cutoff point to predict a poor functional outcome (sensitivity = 59%, specificity = 77%). Patients with perfusion lesion ≥ 65 mL, compared with patients with perfusion lesion <65 mL, showed a much higher rate of poor functional outcome

(38% vs 11%, p < 0.001) [52]. Therefore, favorable perfusion mismatch profile could be used for MT consideration. Successful reperfusion was also found to be an independent predictor for good outcomes [53,54]. Younger age, lower presenting NIHSS score, IV tPA, and absence of hyperglycemia were also independently associated with a favorable outcome in LVO patients with minor strokes [54].

Large Infarct Core

MT for acute stroke due to LVO in the anterior circulation has been limited to patients with a small- to moderate-sized ischemic core at presentation. Among those landmark RCTs for LVO, imaging selection criteria included ASPECTS >5 in ESCAPE and >7 in REVASCAT, ischemic core <50 ml or ASPECTS >6 in SWIFT-PRIME, ischemic core <70 ml in EXTEND-IA and DEFUSE-3. Current guideline recommends ASPECTS ≥ 6 in early window and ischemic core <70 ml in the extended window LVO cases [1].

However, recent 3 RCTs have challenged this concept [55] (**Table 4**). Published in 2022, RESCUE-Japan LIMIT trial enrolled 203 LVO patients at ICA or M1 with ASPECTS 3-5, and randomly assigned equally to MT vs. BMM alone within 6 hours of onset or within 24 hours if no early ischemic changes on FLAIR images. 31% patients in MT group achieved mRS 0-3 at 90 days comparing with 12.7% in the BMM alone group (P=0.002). However, any ICH occurred in 58% and 31.4%, respectively (P<0.001) [56].

A year later, two more RCTs further confirmed this finding (**Table 4**). SELECT-2 trial included a total of 352 patients with LVO at ICA and M1 with ASPECTS 3-5 or ischemic core > 50 ml, who were assigned randomly at 1:1 ratio to MT or BMM only within 24 hours of onset. The trial was stopped early for efficacy. 90-day mRS distribution shifted toward better outcomes in favor of MT. 20.3% patients in the MT group and only 7.0% in the BMM alone group gained functional independence (mRS 0-2) (RR 2.97 [95% CI, 1.60 to 5.51]). Mortality and sICH were similar in two groups [57]. The ANGEL-ASPECT trial from China studied 456 patients with LVO at the terminal ICA or M1 with ASPECTS 3-5 or core infarct 70-100 ml. Subjects were randomly assigned at 1:1 ratio to MT or BMM only group within 24 hours of onset. This trial was also stopped early for efficacy. At 90 days, a shift in the distribution of mRS toward better outcomes was observed in favor of MT over BMM. All-cause death and sICH were comparable within two groups [58].

Based on these results, MT is now recommended for AIS patients due to LVO in the anterior circulation who can start treatment within 24 hours of last known well and have a large ischemic core (defined by an ASPECTS of 3-5 or a core volume ≥ 50 ml determined by perfusion CT or diffusion MRI) [55]. In addition, performing MT in LVO patient with large ischemic core can be potentially cost-effective. An economic evaluation study reported that, compared with BMM alone, MT yielded higher lifetime benefit (2.20 vs. 1.41 quality-adjusted life year gains) equivalent to 288 additional days of healthy life per patient, in exchange of only slightly higher lifetime healthcare cost per patient [59]. Gao *et al.* also constructed a Markov Model to simulate the long-term costs and health outcomes. They reported that MT was associated with greater benefits (1.12 vs. 0.25 quality-adjusted life year gains) and the incremental cost could be primarily offset partially by the reduction in costs related to the nursing home care [60].

Although MT provides functional benefit over non-MT in large ischemic stroke patients, a significant proportion of patients suffered substantial disability even with MT. Predictors for a worse outcome in such population were also studied, and it was found that advanced age (≥ 76 years of age) and large core volume (>90 ml) were independent risk factors of poor outcomes and mortality [61].

Table 4. Summary of outcomes in LVO patients with large ischmic cores undergoing MT

reference	author(s)	study type	sample size	patient subgroup	time after stroke onset	comparison	Endpoints	Results	OR/RR (95% CI)	p value
56	Yoshimura *et al*.	RCT	203	ASPECTS 3-5	within 6h or within 24h if no early ischemic changes on FLAIR images	MT vs. BMM	90-day mRS 0-3	31% vs. 12.7%	RR 2.43 (1.35-4.37)*	0.002*
							any ICH	58% vs. 31.4%		<0.001*
57	Sarraj *et al.*	RCT	352	ASPECTS 3-5, ischemic core >=50 mL	within 24h	MT vs. BMM	90-day mRS ordinal analysis		OR 1.51 (1.2-1.89)*	< 0.001*
							90-day mRS 0-2	20.3% vs. 7.0%	RR 2.97 (1.60-5.51)*	
58	Huo *et al.*	RCT	456	ASPECTS 3-5, ischemic core 70-100 mL	within 24h	MT vs. BMM	90-day mRS ordinal analysis		OR 1.37 (1.11-1.69)*	0.004*
							90-day mRS 0-2	30% vs. 11.6%	OR 2.62 (1.69-4.06)*	
							90-day mortality	21.7% vs. 20%	OR 1.00 (0.65-1.54)	0.99
							sICH within 48h	6.1% vs. 2.7%	OR 2.07 (0.79-5.41)	0.12
* statistical significance										

Mismatch Profile

Per current guideline for LVO patients who are MT candidates, no mismatch profile is required if treatment can be initiated within 6 hours of symptom onset [1]. However, some previous landmark RCTs for LVO had required radiographic mismatch profile as one of the inclusion criteria. For example, the SWIFT PRIME trial required ischemic core <50 ml, penumbra >15 ml and mismatch ratio >1.8 [62], while EXTEND-IA trial demanded ischemic core <70 ml, penumbra >10 ml and mismatch ratio >1.2 [63]. In extended window LVO trials, DAWN required clinical mismatch based on the severity of the clinical deficit and the infarct volume [7], while DEFUSE-3 adopted the one from SWIFT PRIME, i.e., ischemic core <50 ml, penumbra >15 ml and mismatch ratio >1.8 [8]. However, in the recent SELECT-2 trial of large infarct core, MT still demonstrated significant benefits comparing with BMM alone in absence of mismatch, including 154 cases of mismatch ratio <1.8 and mismatch volume <15 ml, and 50 cases of mismatch ratio <1.2 and mismatch volume <10 ml [57].

Recently, studies have challenged whether perfusion profile is necessary for LVO patient selection in late windows (**Table 5**). MR CLEAN-LATE trial investigated whether selection of extended window (6-24h from onset) LVO patients for MT could be primarily based on collateral flow on CTA instead of perfusion criteria derived from the DAWN and DEFUSE-3 trials. Candidates were randomized into MT group (n=255) and BMM alone group (n=247). The median mRS at 90 days and mRS shift both favored the MT group. All-cause mortality did not differ significantly between groups, but sICH occurred more often in MT group (7% vs 2%), suggesting that perfusion data may not be necessary in selecting patients for MT [64]. A study involving 104 cases of MT at very late window (>24h from onset) also showed no significant difference in functional outcome at discharge among patients selected with perfusion versus those selected without perfusion imaging [65].

The CLEAR study selected extended window LVO patients for MT based on the non-contrast CT (NCCT) ASPECTS (n=534), CTP (n=752), or MRI (n=318). LVO was confirmed with CTA

Table 5. Summary of outcomes in LVO patients with unfavorable mismatch undergoing MT

reference	author(s)	study type	sample size	patient subgroup	time after stroke onset	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
57	Sarraj *et al.*	RCT	154	mismatch ratio <1.8 and mismatch volume <15 mL	<24h	MT vs. BMM	90-day mRS ordinal analysis		OR 1.85 (1.30-2.58)*	
			50	mismatch ratio <1.2 and mismatch volume <10 mL					OR 2.54 (1.26-5.14)*	
64	Oluthis *et al.*	RCT	502	collateral flow seen on CTA, perfusion study not done	6-24h	MT vs. BMM	90-day median mRS	3 vs. 4	OR 1.42 (1.04-1.93)*	
							90-day mRS ordinal analysis		aOR 1.67 (1.20-2.32)*	
							all-case mortality	24% vs. 30%	aOR 0.72 (0.44-1.18)	
							sICH	7% vs. 2%	OR 4.59 (1.49-14.10)*	
65	Dhillon *et al.*	retrospectiva from registry with 2:1 PSM	104	>24h from stroke onset	>24h	perfusion vs. without perfusion images	mRS at discharge		OR 1.38 (0.81-1.76)	0.18
66	Nguyen *et al.*	multicenter cohort study	1604	MT	6-24h	CT ASPECT vs CTP	90-day mRS ordinal analysis		aOR 0.95 (0.77-1.17)	0.64
						CT ASPECT vs MRI			aOR 0.95 (0.8-1.13)	0.55
						CT ASPECT vs CTP	90-day mRS 0-2		aOR, 0.90 (0.7-1.16)	0.42
						MRI vs. CT ASPECT			aOR, 0.79 (0.64-0.98)*	0.03*
						CT ASPECT vs. CT perfusion vs. MRI	successful reperfusion	88.9% vs. 89.5% vs. 78.9%		<0.001*
							sICH	8.1% vs. 5.8% vs. 4.7%		0.11
							90-day mortality	23.4% vs. 23.1% vs. 19.5		0.38
67	Olivot *et al*.	multicenter cohort study	218	MT	<6h	target mismatch # vs. non target mismatch	90-day mRS 0-2	61% vs. 35%	OR 3.3 (1.4-7.9)*	0.007*
						mismatch $ vs. no mismatch		58% vs. 38%	aOR 5.9 (1.8–19.6)*	0.004*

target mismatch (core <70, ration >1.2, volume >10mL); $ mismatch (ratio >1.2 and volume >10); PSM: propensity score matching

* statistical significance

or MRA in most patients. No significant difference in 90-day ordinal mRS shift was observed between patients selected by NCCT vs CTP or NCCT vs MRI. sICH and 3-month mortality rates were also comparable between the groups [66]. The authors therefore boasted a simpler NCCT ASPECTS to widen the LVO patient candidacy in the extended time window. However, limitations of this study include retrograde cohort design, inconsistent neuroimaging protocol, and unblinded assessment.

Nonetheless, there are studies which have questioned the benefits of MT in LVO patients if absence of mismatch. For instance, Olivot *et al.* reported that without mismatch, reperfusion (TICI 2b/c-3) was not associated with increased rate of functional recovery, and even demonstrated a trend towards a worse outcome than no reperfusion (TICI 0-2a) [67]. However, this study's sample size was relatively small.

Time Window

While 24 hours after stroke onset is the cutoff time for performing MT in current stroke guideline [1], new evidence shows that some patients may be able to benefit from MT beyond this timeframe if their infarcts are developing slowly. Christensen *et al*. examined the DEFUSE-3 data and found that 18% of patients in the control arm of this study had a persistent mismatch on CT perfusion for an average of 38 hours from presentation. These patients had lower hypoperfusion index scores, indicating that they had good collateral flow to the affected tissue [68]. While these patients did not receive MT and tended to have poor clinical outcomes, their persistent mismatches raise the question of whether similar patients could benefit from very late MT.

A small cohort study of 43 patients with both anterior and posterior strokes treated with MT >24 hours from onset found that functional independence was achieved in about 25% of cases. In cases where reperfusion was not achieved, no patients had a favorable functional outcome [69]. Some studies have directly compared MT with BMM in those LVO patients beyond 24 hours of last known well but with qualified mismatch (**Table 6**). In the SELECT Late retrospective study of 301 such patients, Sarraj *et al.* found MT was associated with higher odds of functional independence (mRs 0-2) and lower odds of mortality than BMM, despite increased odds of sICH [70]. These patients all had persistent perfusion mismatches, demonstrating the potential need for MT beyond 24 hours.

More studies have compared the effects of MT in the very late time window (>24 hours) with those in the extended time

Table 6. Summary of outcomes in LVO patients undergoing MT beyond 24 hours of stroke onset

reference	author(s)	study type	sample size	patient subgroup	comparison	endpoint(s)	results	OR/RR	p value
69	Purrucker *et al.*	retrospective analysis of registry data	43	>24 hours from stroke onset	reperfusion vs. non-reperfusion	90-day mRS 0-2 or ROR	29.4% vs. 0%		
			2347	MT	MT >24 hours vs. <24 hours	90-day mRS 0-2 or ROR	23.3% vs. 39.4		0.04*
70	Sarraj *et al.*	multicenter cohort study	301	>24 hours from stroke onset	MT vs. BMM	90-day mRS 0-2	38.1% vs. 10.4%	aOR 4.56 (2.28-9.09)*	<0.01*
						sICH	10.1% vs. 1.8%	aOR 10.65 (2.19-51.69)*	0.003*
						90-day mortality	26% vs. 40.9%	aOR 0.49 (0.27-0.89)*	0.02*
72	Desai *et al.*	retrospective	21 + 107 (from DAWN)	>24 hours from stroke onset but otherwise meeting DAWN criteria	MT > 24h vs. DAWN intervention arm	90-day mRS 0-2	43% vs. 48%		0.68
						sICH	5% vs. 6%		0.87
						recannalization	81% vs. 84%		0.72
65	Dhillon *et al.*	retrospectiva from registry with 2:1 PSM	312	>24 hours from stroke onset	MT >24h vs. 6-24h	discharge mRS ordinal analysis		OR 1.08 (0.69-1.47)	0.7
						discharge mRS 0-2	28.8% vs. 29.3%	OR 0.97 (0.58-1.64)	0.93
						sICH	4.8% vs. 8%		0.43
73	Shaban *et al.*	retrospective from registry with 2:1 PSM	363	>24 hours from stroke onset	MT >24h vs. 6-24h	90-day mRS 0-2	18.8% vs. 34.9%	0.24 (0.11-0.52)*	<0.001*
						90-day mortality	31.1% vs. 22%	OR 2.34 (1.13-4.84)*	0.023*
						sICH		OR 0.52 (0.19-1.44)	0.209

ROR: reture of Rankin; PSM: propensity score matching
* statistical significance

window (6-24 hours) (**Table 6**). In a study using 2:1 propensity-score matched individual level data from a UK national stroke registry, Dhillon *et al.* found that patients receiving MT in the very late time window had similar functional outcomes to patients receiving MT in the extended time window (28.8% vs. 29.3%, mRS of 0-2 at discharge) [65]. The rates of successful reperfusion, sICH, and in-hospital mortality were also of no significant difference between the two different time windows. However, the long-term functional outcomes such as mRS at 90 days were not reported. In a meta-analysis of 7 studies with a total of 569 patients, MT performed after an average of 46.2 hours from onset resulted 81.9% revascularization with TICI scores of 2b or better, and 32% favorable outcome of mRS 0-2 at 90 days [71]. Only 6.8% of the patients in this analysis developed sICH, demonstrating acceptable efficacy and safety outcomes of MT after 24 hours, similar to those from patients receiving MT in earlier windows. In a small retrospective review of 21 cases from 3 large comprehensive stroke centers meeting DAWN criteria but presenting outside the 24-hour window, 43% of such patients had a mRS of 0-2 at 90 days after MT compared with 48% of patients in the DAWN trial intervention arm [72]. Successful reperfusion rates were also comparable (81% vs. 84%), so was the complication of sICH (5% vs. 6%). These studies support that MT is safe and feasible in patients with LVO and favorable mismatch profile but beyond 24 hours of stroke onset.

In contrast, a report with a 2:1 matched group of patients showed that patients receiving MT at the very late time window were less likely to be independent at 90 days than those at extended time window [73]. They also had higher odds of mortality at 90 days, but sICH and other complications were similar in the two groups. In another retrospective study of 2347 cases, favorable outcome was achieved less in the MT > 24 h group compared with the MT < 24 h group (23.4% vs. 39.4%, p = 0.04) although bleeding and mortality rates were similar between groups [69]. Therefore, although performing MT >24 hours after stroke onset may be safe and feasible, the benefit towards functional outcome still warrants further investigation.

Posterior Circulation LVO

Most clinical trials on MT in LVO stroke have focused on patients with infarcts of the anterior circulation. This is reasonable given that basilar artery occlusion (BAO) is rare, representing only about 1% of ischemic strokes. However, patients with BAO are usually critical with severe deficit, and may also benefit from MT. The current guideline is uncertain about the benefit of MT in posterior LVOs but feels MT may be reasonable in carefully selected BAO patients within 6 hours of onset [1]. This concept is finally established recently with several clinical trials demonstrating MT is safe and potentially effective in BAO [74] (**Table 7**).

In the BEST trial, patients with BAO were randomized within 8 hours of onset to receive either MT or BMM [75]. However, the study was terminated early due to high crossover rate and poor enrollment. A total of 131 subjects were included, and there was no statistical difference of mRS 0-3 at 3 months or 90-day mortality between the two groups in the intention-to-treat analysis. Nonetheless, it did show higher rates of mRS 0-3 at 90 days in patients with MT than with BMM alone in as-treated analysis [75]. Similarly, in the BASICS trial with 300 stroke patients due to BAO randomized within 6h of onset to undergo MT or BMM, it was found that good functional outcomes (mRS 0-3 at 3 months) or 90-day mortality rates were not significantly different from the two groups [76]. Both trials also showed higher rate of sICH in the intervention group [75,76]. Despite numerical differences in favor of MT, these trials did not show the superiority of MT over BMM alone. However, there were high rates of crossovers, poor recruitment, and early termination in the BEST trial [75] and a lack of consecutive enrollment in BASICS [76], which limited the certainty of their results. However, the trials suggested a potential benefit of MT in a subgroup of patients presenting with moderate-to-severe symptoms (NIHSS ≥10).

Subsequently, two Chinese clinical trials, the ATTENTION and the BAOCHE trials, made progress in MT treatment of BAO with modified patient selection. The ATTENTION trial compared MT with BMM (2:1 ratio) in 340 patients with BAO and NIHSS ≥10 who presented up to 12 hours after stroke onset [77]. They found that good functional recovery was more likely in patients treated with MT and that 90-day mortality was significantly lower in this group as well. However, rates of sICH were still higher in the MT group (5% vs. 0%) [77]. The BAOCHE trial studied 217 BAO patients with NIHSS ≥ 6 and up to 24h after stroke onset. Again, it revealed that good outcome occurred more frequently in patients treated with MT than those treated with BMM alone, although with higher rates of sICH in patients treated with MT (6% vs 1%) [78]. Taken together, MT appears to benefit BAO patients with moderate to-severe symptoms and should be offered to eligible candidates.

For MT on isolated posterior cerebral artery (PCA) occlusion (PCAO), however, the conclusion is not quite clear (**Table 7**). Recent systemic reviews and meta-analysis showed MT is safe for PCAO, but there is no significance in odds of favorable outcome, sICH, and mortality between MT and BMM only, despite superior recanalization rates in MT group [79,80]. Lately, a retrospective study of 752 PCAO (including P1 and P2 segments) patients using propensity score weighting showed that MT was not associated with good or excellent functional outcome as compared to BMM, but instead was associated with higher rates of sICH and early neurological deterioration [81]. Similarly, using propensity score matching, the TOPMOST study studied 184 matched distal PCAO (P2 and P3 segments) patients and found no difference in 90-day mRS and sICH between MT and BMM groups. However, it did show that MT was associated with higher reduction of NIHSS at discharge (average 1.5 points) than BMM alone, and that MT may potentially benefit subgroup of PCAO patients with NIHSS ≥

Table 7. Summary of outcomes in patients with posterior circulation LVO undergoing MT

reference	author(s)	study type	sample size	time after stroke onset	patient subgroup	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
75	Liu *et al.*	RCT open label	131	< 8h	vertebrobasilar LVO	MT vs. BMM	90-day mRS 0-3 intention to treat	42% vs. 32%	aOR 1.74 (0.81-3.74)	
							90-day mRS 0-3 pre-protocol	44% vs. 25%	aOR 2.90 (1.20-7.03)*	
							90-day mRS 0-3 as treated	47% vs. 24%	aOR 3.02 (1.31-7.00)*	
							90-day mortality	33% vs. 38%		0.54
76	Langezaal *et al.*	RCT open label	300	< 6h	BAO	MT vs. BMM	90-day mRS 0-3	44.2% vs. 37.7%	RR 1.18 (0.92-1.5)	0.19
							90-day mortality	38.3% vs. 43.2%	RR 0.87 (0.68-1.12)	
							sICH	4.5% vs. 0.7%	RR 6.9 (0.9-53.0)	
77	Tao *et al.*	RCT open label 2:1 ratio	340	< 12h	BAO with NIHSS >= 10	MT vs. BMM	90-day mRS 0-3	46% vs. 23%	aRR 2.06 (1.46-2.91)*	<0.001*
							90-day mortality	37% vs. 55%	aRR 0.66 (0.52 to 0.82)*	
78	Jovin *et al.*	RCT open label	217	6-24h	BAO with NIHSS >= 6	MT vs. BMM	90-day mRS 0-3	46% vs. 24%	aRR 1.81 (1.26-2.6)*	< 0.001*
							sICH	6% vs. 1%	RR 5.18 (0.64-42.18)	
							90-day mortality	31% vs. 42%	aRR 0.75 (0.54 to 1.04)	
79	Berberich *et al.*	systematic review and meta-analysis	679		isolated PCAO	MT vs. BMM	90-day mRS 0-2	58% vs. 48.1%		
							90-day mortality	12.6% vs. 12.3%		
							sICH	4.2% vs. 3.2%		
80	Montiero *et al.*	systematic review	265		isolated PCAO	MT vs. tPA alone	90-day mRS 0-2	59.1% vs. 48.4%	OR 1.5 (0.8-2.5)	
							90-day mortality	10.7% vs. 5.3%	OR 1.4 (0.5-3.6)	
							sICH	3.5% vs. 3.0%	OR 1.1 (0.2-5.5)	
							recannalization	85.6% vs 53.1%		p<0.00001*
81	Sabben *et al.*	retrospective with PSW	752		proximal PCAO (P1+P2)	MT vs. BMM	90-day mRS 0-2	58.1% vs. 65.5%	OR 0.81 (0.66-1.01)	0.06
							90-day mRS 0-1	41.9% vs. 43.4%	OR 1.17 (0.95-1.43)	0.15
							sICH	4.8% vs. 2.1%	OR 2.51 (1.35-4.67)*	0.004*
							NIHSS increase >=4 at 24h	14.2% vs. 4.7%	OR 2.51 (1.64-3.84)*	<0.0001*
82	Meyer *et al.*	retrospective with PSM	184		distal PCAO (P2+P3)	MT vs. BMM	90-day mRS 0-2	76.6% vs. 75.4%		0.87
							sICH	4.3% vs. 4.3%		>0.99
							decrease in NIHSS at discharge	-3.9 vs. -2.4		0.06
						MT vs. BMM in NIHSS >=10	decrease in NIHSS at discharge	-9.5 vs. -3.9		0.04
83	Nguyen *et al.*	retrospective	1023	<24h	PCAO	MT vs. BMM	90-day mRS 0-1	32.3% vs. 26.7%	aOR 1.50 (1.07-2.09)	0.018*
							90-day mRS 0-2	51% vs. 53.3%	aOR 1.06 (0.78-1.46)	0.696
							90-day mRS ordinal analysis		aOR 1.13 (0.85-1.50)	0.413
							sICH	6.2% vs. 1.7%		0.0001*
							90-day mortality	10.1% vs. 5%		0.002*

PSW: propensity score weighting; PSM: propensity socre matching

* statistical significance

10 or who were not treated with tPA [82]. In the recent PLATO study, a large case-control study of 1023 patients, Nguyen *et al*. revealed that decreases in NIHSS ≥ 2 points, excellent outcome (mRS 0-1) and complete vision recovery were more common in patients treated with MT than those who received BMM only [83]. However, no significant difference was found in functional independence (mRS 0-2), and patients who received MT had a greater chance of developing sICH. Obviously, RCTs of MT in this population are urgently needed. When we design future RCTs for PCAO, the efficacy endpoint should include vision recovery in addition to the mRS analysis when comes to the outcome measures.

Distal Medium Vessel Occlusions

Distal medium vessels are defined as cerebral arteries with lumen diameters between 0.75 and 2.0 mm, which generally include M3 and M4 MCA segments, A2 to A5 anterior cerebral artery (ACA) segments, and P2 to P5 PCA segments with M2 MCA segment varying in size [84]. While the proximal large cerebral vessels are current MT treatment targets, distal medium vessels have become the next potential target for MT. Outcomes for distal medium vessel occlusion (DMVO) are generally better compared with more proximal LVOs, but many patients still suffer from severe disability [84]. IV

thrombolysis was able to recanalize about 40-50% of distal medium vessels [85-87]. However, it was early recanalization, not IV thrombolysis, that dictated the excellent functional outcome [85].

DMVOs were initially excluded from clinical MT trials, largely due to vessel tortuosity and smaller caliber. The current guideline states that MT may be reasonable for carefully selected patients in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, although the benefits are uncertain [1]. Although MT for DMVO has not been established as a standard of care, it is time to revisit this topic as endovascular technology has rapidly advanced.

In the original landmark RCTs for LVO, there were limited cases of M2 MCA occlusions. In a HERMES pooled analysis, 130 patients with M2 occlusions were included in 7 randomized clinical trials. Successful reperfusion was achieved in 59% in MT group. Compared with BMM alone, MT showed significant 90-day functional independence (58% vs 40%; P=0.03). Interestingly, 0% sICH was observed in MT group compared with 7.9% in controls [88].

Beyond M2 segment of MCA, evidence for MT on other DMVOs is primarily from retrospective studies (**Table 8**). Grossberg *et al*. reported a cohort of 69 patients with DMVO (M3, ACA and PCA) who received MT with 83% successful reperfusion (TICI2b-3), 20% 90-day functional recovery (mRS 0-2), 4% ICH and 20% mortality at 3 months [89]. Recent systemic review of 1262 DMVO patients who underwent MT showed 84% successful reperfusion (TICI2b-3), 64% 90-day functional recovery (mRS 0-2), 12% ICH and 6% mortality at 3 months in primary DMVOs, with similar results in secondary DMVOs [90]. It appeared that the MT on DMVOs was safe and feasible.

As mentioned in the previous section, the TOPMOST study included 184 matched patients with PCA P2 and P3 segment occlusions and reported no difference in functional or safety outcomes between MT and BMM. However, it did show that MT may potentially benefit more severe PCAO patients with NIHSS ≥ 10, but not minor PCAO strokes [82]. A systematic review and meta-analysis evaluating the efficacy and safety of MT versus BMM in primary DMVO was also performed with 1202 patients receiving MT and 1267 patients receiving BMM only. MT group achieved significantly better odds of functional independence (mRS 0-2) than BMM. There were no significant differences in excellent functional outcome (mRS 0-1), sICH or 90-day mortality [91]. Of note, in minor strokes (NIHSS <6), MT was associated with significantly more sICH (OR 6.30 [95% CI, 1.55 to 25.64]), again indicating risks may overweigh benefit in DMVO patients with minor strokes. Further investigation with well-designed randomized controlled trials is necessary.

Some authors also compared efficacy and safety outcomes of MT in DMVO vs. LVO (**Table 8**). The analysis included 1032 patients (147 DMVO and 885 LVO) patients within the ANGEL-ACT Registry and showed similar rates of 90-day mRS distribution, sICH and successful recanalization between two groups [92]. The study also identified that baseline NIHSS ≤ 14 (OR 1.96 [95% CI, 1.02 to 3.80], p=0.045) and successful MT with one pass (OR 2.16, [95% CI, 1.14 to 4.11], p=0.021) were independent predictors of the 90-day good outcome in DMVO patients undergoing MT.

Table 8 Summary of outcomes in patients with distal medium vessel occlusions undergoing MT

reference	author(s)	study type	sample size	patient subgroup	comparison	endpoint(s)	results	OR/RR (95% CI)	p value
88	Menon *et al.*	retrospective	130	M2 segment occlusions	MT vs. BMM	90-day mRS 0-2	58.2% vs. 39.7%	OR 2.39 (1.08-5.28)	0.03*
						sICH	0 vs. 7.9%		
82	Meyer *et al.*	retrospective with PSM	184	distal PCAO (P2+P3)	MT vs. BMM	90-day mRS 0-2	76.6% vs. 75.4%		0.87
						sICH	4.3% vs. 4.3%		>0.99
						decrease in NIHSS at discharge	-3.9 vs. -2.4		0.06
					MT vs. BMM in NIHSS >=10	decrease in NIHSS at discharge	-9.5 vs. -3.9		0.04
91	Loh *et al.*	syetemic review and meta-analysis	2469	primary DMVO	MT vs. BMM	90-day mRS 0-2		OR 1.61 (1.06-2.43)*	0.024*
						90-day mRS 0-1		OR 1.23 (0.88-1.71)	
						90-day mortality		OR 1.03 (0.73-1.45)	
						sICH		OR 1.44 (0.78-2.66)	
92	Sun *et al.*	retrospective from registry	1032	MT	DMVO vs. LVO	90-day median mRS	3 vs. 3	OR 1.00 (0.73-1.38)	0.994
						90-day mRS 0-2	44.9% vs. 45.0%	OR 0.90 (0.62-1.31)	0.589
						sICH	4.8% vs. 8.9%	OR 0.59 (0.26-1.34)	0.205
						recannalization	89.8% vs. 89.7%	OR 1.00 (0.51-1.9)	0.992

* statistical significance

Summary

It is important for healthcare professionals to adhere to established guidelines and protocols, and to stay updated on the new developments and advancements in stroke care. More and more recent studies have included several unique subgroups of LVO patients that previously were excluded from MT based on current acute stroke guidelines. Compared with BMM alone, almost all these subgroup patients achieved better functional outcomes with comparable adverse events, although some of them are still controversial. Although this suggests a more widespread use of MT beyond the current strict guidelines is possible, we do need more well-designed RCTs in the abovementioned stroke subgroups to reproduce the promising results that we have found in the retrospective studies. We also invite more prospective studies designed to answer several urgent questions, such as identifying predictive factors that are associated with futile reperfusion, hemorrhagic conversion, or rapid/slow stroke progression. This can eventually assist in creating the subgroup-specific criteria to select more appropriate candidates in whom the benefits of MT outweigh the risks, so that decisions about individual patient care could be tailored based on the specific circumstances of each case. We believe that the future LVO endovascular therapy will be not only more effective but also more inclusive.

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