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Medical Management vs Mechanical Thrombectomy for Mild Strokes
An International Multicenter Study and Systematic Review and Meta-analysis

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IMPORTANCE The benefit of mechanical thrombectomy (MT) in patients with stroke presenting with mild deficits (National Institutes of Health Stroke Scale [NIHSS] score <6) owing to emergency large-vessel occlusion (ELVO) remains uncertain.

OBJECTIVE To assess the outcomes of patients with mild-deficits ELVO (mELVO) treated with MT vs best medical management (bMM).

DATA SOURCES We retrospectively pooled patients with mELVO during a 5-year period from 16 centers. A meta-analysis of studies reporting efficacy and safety outcomes with MT or bMM among patients with mELVO was also conducted. Data were analyzed between 2013 and 2017.

STUDY SELECTION We identified studies that enrolled patients with stroke (within 24 hours of symptom onset) with mELVO treated with MT or bMM.

MAIN OUTCOMES AND MEASURES Efficacy outcomes included 3-month favorable functional outcome and 3-month functional independence that were defined as modified Rankin Scale scores of 0 to 1 and 0 to 2, respectively. Safety outcomes included 3-month mortality and symptomatic and asymptomatic intracranial hemorrhage (ICH).

RESULTS We evaluated a total of 251 patients with mELVO who were treated with MT (n = 138; 65 women; mean age, 65.2 years; median NIHSS score, 4; interquartile range [IQR], 3-5) or bMM (n = 113; 51 women; mean age, 64.8; median NIHSS score, 3; interquartile range [IQR], 2-4). The rate of asymptomatic ICH was lower in bMM (4.6% vs 17.5%; $P = .002$), while the rate of 3-month FI (after imputation of missing follow-up evaluations) was lower in MT (77.4% vs 88.5%; $P = .02$). The 2 groups did not differ in any other efficacy or safety outcomes. In multivariable analyses, MT was associated with higher odds of asymptomatic ICH (odds ratio [OR], 11.07; 95% CI, 1.31-93.53; $P = .03$). In the meta-analysis of 4 studies (843 patients), MT was associated with higher odds of symptomatic ICH in unadjusted analyses (OR, 5.52; 95% CI, 1.91-15.49; $P = .002$; $I^2 = 0\%$). This association did not retain its significance in adjusted analyses including 2 studies (OR, 2.06; 95% CI, 0.49-8.63; $P = .32$; $I^2 = 0\%$). The meta-analysis did not document any other independent associations between treatment groups and safety or efficacy outcomes.

CONCLUSIONS AND RELEVANCE Our multicenter study coupled with the meta-analysis suggests similar outcomes of MT and bMM in patients with stroke with mELVO, but no conclusions about treatment effect can be made. The clinical equipoise can further be resolved by a randomized clinical trial.

Supplemental content

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American Heart Association (AHA) recommendations outline that mechanical thrombectomy (MT) is standard of care for anterior circulation emergency large-vessel occlusion (ELVO) presenting with National Institutes of Health Stroke Scale (NIHSS) scores of at least 6 points during the first 6 hours from symptom onset and during 6 to 24 hours from symptom onset in selected patients who fulfill advanced neuroimaging criteria.[1] Because randomized clinical trials[2-5] excluded patients with ELVO presenting with low NIHSS scores (0-5 points), except 10 patients in the Multicenter Randomized Clinical Trial of the Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)[6] and 4 patients in Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA)[7] trials, the efficacy and safety of MT in this cohort are lacking. Previous studies involving patients with ELVO with mild deficits have demonstrated worse outcomes among patients with acute ischemic stroke (AIS) not treated with either intravenous thrombolysis (IVT) or MT.[8-10]

Up to 10% of patients with ELVO presenting within 6 hours can have mild deficits,[11] and because of fragile collateral status, they can deteriorate rapidly or gradually, leading to poor outcome.[12] The treating physicians often find themselves in a conundrum of whether to treat this subgroup of patients with ELVO with MT. Some multicenter studies have evaluated the role of MT in patients with ELVO with low NIHSS scores (<6 points; mELVO) and suggested a potential benefit of MT.[10,13] On the other hand, other investigators have reported equivalent safety and efficacy outcomes in results between MT and best medical management (bMM) in mELVO.[14-16]

In view of these conflicting observational reports and owing to the lack of randomized data, we conducted an international multicenter study to compare safety and efficacy outcomes in patients with mELVO treated with MT or bMM. We also performed a systematic review and meta-analysis to further comparatively evaluate the safety and effectiveness of MT vs bMM among patients with AIS with mELVO.

Key Points

Question Is mechanical thrombectomy superior to best medical management (bMM) for mild-deficits emergency large-vessel occlusion (mELVO) strokes?

Findings In this pooled analysis of 251 patients with mELVO, we documented higher odds of asymptomatic intracerebral hemorrhage with mechanical thrombectomy compared with bMM. The systematic review and meta-analysis of 4 studies did not document any independent association between treatment groups and safety or efficacy outcomes.

Meaning Mechanical thrombectomy has a similar efficacy and safety profile compared with bMM in patients with stroke with mELVO.

Methods

Consecutive patients with AIS with mELVO were retrospectively identified from registries collecting prospective data of 16 high-volume endovascular stroke centers in North America, Europe, and Asia during a 5-year period (2013-2017). The data were pooled to analyze and determine the safety and efficacy outcomes in patients with mELVO treated with 2 different therapeutic approaches: bMM (including treatment with intravenous thrombolysis [IVT]) and MT (with or without pretreatment with IVT). All patients with AIS fulfilling the following criteria were included in this study: (1) patients with anterior circulation ELVO (internal carotid artery, M1 middle cerebral artery, and M2 middle cerebral artery) diagnosed and treated within 24 hours from symptom onset; (2) admission NIHSS score of less than 6 points; (3) treatment period ranging between January 1, 2013, and June 31, 2017; (4) prestroke modified Rankin Scale (mRS) score of 0 to 1; (5) no history of prior stroke; and (6) being 18 years or older. Further details of study selection are available in the eMethods of the Supplement.

We recorded the following baseline characteristics as previously described in other reports of our international collaborative group[17-19]: age, race/ethnicity, sex, hypertension, diabetes, hyperlipidemia, coronary artery disease, end-stage renal disease, smoking status, admission blood pressure levels, prior antiplatelet use, prior anticoagulant use, Alberta Stroke Program Early Computed Tomography (CT) score, admission and discharge NIHSS scores, location of occlusion, good collaterals on baseline CT angiography, and pretreatment with IVT. Collateral score (CS) for anterior-circulation ELVO was reported in a dichotomized fashion (ie, poor [CS = 0 or 1] vs good [CS = 2, 3, and 4]) using American Society of Interventional and Therapeutic Neuroradiology methods that have been shown to predict outcomes.[20]

We evaluated the following efficacy outcomes: 3-month functional independence (FI) defined as mRS scores of 0 to 2 at 90 days, 3-month favorable functional outcome (FFO) defined as mRS scores of 0 to 1 at 90 days, distribution of mRS scores at discharge and at 90 days, neurological improvement during hospitalization defined as the decrease in the baseline NIHSS score at hospital discharge (baseline NIHSS score minues discharge NIHSS score), successful reperfusion, length of intensive care unit stay, and length of hospital stay. The safety end points included 3-month all-cause mortality, symptomatic intracranial hemorrhage (sICH) defined as presence of a parenchymal hematoma type 2 on postinterventional brain CT or magnetic resonance imaging, accounting for deterioration with an increase in NIHSS score of at least 4 points within 36 hours from treatment as previously described,[19] and asymptomatic intracranial hemorrhage including all remaining nonsymptomatic intracranial hemorrhages. All certified vascular neurologists performed evaluations of stroke severity and residual disability at 3 months as part of their clinical duties. There was no central adjudication of clinical outcomes.

Our systematic review and meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses, and data were presented according to the Meta-Analysis of Observational Studies Epidemiology (MOOSE) proposal.[21,22] We identified studies using

MEDLINE and SCOPUS databases. The complete search algorithm used in MEDLINE search is available in the eMethods of the Supplement. No language or other search restrictions were applied. We included trials if they enrolled patients with AIS (within 24 hours of symptom onset) with ELVO and mild neurological severity (NIHSS ≤5) for MT (intra-arterial thrombolysis and MT alone or in combination) or medical treatment with or without IVT. The risk of bias of included studies was evaluated using the Newcastle-Ottawa Scale as previously described.[23]

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the relevant ethics committees of individual centers. Owing to the nature of this retrospective medical record review study, the institutional review boards waived the need for patients' consent.

Statistical Analyses

A detailed statistical analyses subsection is available in the eMethods of the Supplement. We compared the baseline characteristics and outcomes among patients with AIS with mELVO treated with either MT or bMM. In multivariable regression analysis, we adjusted for a priori defined confounders of age, admission NIHSS score, pretreatment with IVT, admission glucose, admission systolic blood pressure, collateral status, and Alberta Stroke Program Early CT Score on baseline neuroimaging. We also performed alternative multivariable analyses using as confounders all baseline characteristics that contributed to the outcome of interest in the initial univariable analyses at *P* values less than .10.

We also performed ordinal regression analysis on discharge and 90-day functional outcome to identify independent factors associated with functional improvement defined as 1-point decrease in the mRS score in a shift analysis.[18] To confirm the findings of the aforementioned regression models, we performed additional sensitivity analyses on the outcomes of interest in propensity score–matched (PSM) groups. Patients in the active group (MT treatment) were matched to control group patients (bMM) using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between the 2 aforementioned groups.

Sensitivity analyses involved the use of both regression-based multiple imputation and last-observation carried forward (LOCF) imputation of missing 3-month follow-up evaluations. We also conducted additional subgroup analyses stratified by location of occlusion (proximal vs distal) and baseline stroke severity (4-5 points in NIHSS score vs 0-3 points).

In our meta-analysis, we calculated relative odds ratios (ORs) and their corresponding 95% confidence intervals to measure the effect size of all the outcomes. We also performed sensitivity analyses according to the status of 3-month follow-up evaluations after excluding patients with missing 3-month mRS scores. We additionally performed adjusted analyses for those studies that provided OR of MT vs bMM after adjusting for confounding variables. A random-effects model (Der Simonian Laird) was used to calculate the pooled OR in both the overall and subgroup analyses.[24] We performed equivalent *z* test for each pooled OR, and a 2-tailed *P* value less than .05 was considered statistically significant. We also performed sensitivity analysis by excluding the patients who were lost to follow-up to effectively compare our retrospective cohort with the findings of meta-analysis.

Results

A total of 251 consecutive patients with mELVO were included in our study; 138 received treatment with MT (mean [SD] age, 65.2 [16.6] years, 47.1% women [n = 65 of 138], median baseline NIHSS score, 4 points; interquartile range, 3-5); 113 patients received treatment with bMM (mean [SD] age, 64.8 [12.8] years; 45.1% women [n = 51 of 113]; median baseline NIHSS score, 3 points; interquartile range, 2-4). **Table 1** compares baseline characteristics in the 2 treatment groups. Proximal occlusions were more common in patients with mELVO treated with MT (75.3% vs 60.2%; *P* = .01). Intravenous thrombolysis tended to be more common in patients receiving MT (53.6% [n = 74 of 138] vs 40.7% [n = 46 of 113]; *P* = .05), whereas current smoking was more prevalent in patients with bMM (39.8% [n = 45 of 113] vs 26% [n = 36 of 138]; *P* = .02). Finally, median admission NIHSS scores were higher in the MT group (4 vs 3 points; *P* < .001).

Table 2 presents safety and efficacy outcomes in the 2 treatment groups. In unadjusted analyses, patients treated with bMM had lower rates of asymptomatic ICH (4.6% [n = 5 of 109] vs 17.5% [n = 24 of 137]; *P* = .002), lower median mRS scores at hospital discharge (1; interquartile range, 0-2 vs 1; interquartile range, 1-3; *P* = .002), and shorter median length of hospital stay (4 days; interquartile range, 3-7 vs 5 days; interquartile range, 4-9; *P* = .002). The 2 groups did not differ in terms of sICH (4.4% vs 0.9%; *P* = .11), neurological improvement during hospitalization (2 points; interquartile range, 1-3 vs 1 point; interquartile range, 0-3; *P* = .69), 3-month FFO (63.1% vs 70.4%; *P* = .26), 3-month FI (76.7% vs 85.2%; *P* = .12); 3-month mortality (9.7% vs 5.7%; *P* = .28); and distribution of 3-month mRS scores (median, 1; interquartile range, 0-2; vs 1; interquartile range, 0-2; *P* = .09). The analyses after imputation of missing data using LOCF methods showed that patients treated with bMM had higher rates of 3-month FI (mRS 0-2: 88.5% vs 77.4%; *P* = .02), but the 2 groups did not differ in the distribution of 3-month mRS scores, the rate of 3-month FFO, and 3-month mortality. After regression-based imputation of missing 3-month functional outcome data, no differences in the probability of FFO (OR, 0.72; 95% CI, 0.41-1.26; *P* = .24), FI (OR, 0.59; 95% CI, 0.30-1.17; *P* = .13), mortality (OR, 1.50; 95% CI, 0.53-4.26; *P* = .44), or mRS distribution (common OR, 0.73; 95% CI, 0.45-1.18; *P* = .20) were detected between MT and bMM groups.

An overview on the distribution of missing variables in baseline characteristics and outcomes between the 2 groups is available in eTable 1 in the Supplement. Three-month functional outcome evaluations were missing in 4% (n = 6 of 138)

Table 1. Baseline Characteristics of the Study Population

Baseline Characteristic	No./Total No. (%)		P Value
	Mechanical Thrombectomy (n = 138)	Best Medical Management (n = 113)	
Age, mean (SD), y	65.2 (16.6)	64.8 (12.8)	.85
Female	65/138 (47.1)	51/113 (45.1)	.76
Hypertension	103/138 (74.6)	80/113 (70.7)	.50
Diabetes mellitus	39/135 (28.9)	29/112 (25.9)	.60
Hyperlipidemia	66/138 (47.8)	54/113 (47.8)	>.99
Atrial fibrillation	40/136 (29.4)	24/113 (21.2)	.14
Coronary artery disease	23/138 (17.4)	30/113 (27.4)	.06
Congestive heart failure	14/121 (11.5)	15/113 (13.2)	.69
End-stage renal disease	7/126 (5.5)	2/111 (1.8)	.13
Current smoking	36/138 (26.1)	45/112 (40.1)	.02
Admission, mean (SD)			
Glucose level, mg/dL	126.7 (44.8)	136.5 (64.0)	.16
SBP, mm Hg	147.9 (22.5)	147.8 (31.0)	.99
DBP, mm Hg	83.3 (14.4)	82.7 (20.3)	.81
Pretreatment, %			
Antiplatelet	50.7	39.8	.34
Anticoagulant	18.1	13.4	.58
NIHSS admission, median (IQR)	4 (3-5)	3 (2-4)	<.001
ASPECTS admission, median (IQR)	10 (9-10)	9 (8-10)	.67
Good collaterals on CTA[a]	80/99 (81.8)	49/61 (80.3)	.81
Disability prior stroke, %	22.9	27.0	.49
IVtPA	74/137 (54.0)	47/113 (41.5)	.05
Onset to tPA, median (IQR), min	120 (85-165)	120 (90-180)	.97
Onset-to-groin puncture time, median (IQR), min	219 (165-397)	NA	NA
Groin puncture-to-reperfusion time, median (IQR), min	44 (31-67)	NA	NA
Drip and ship	30/138 (21.7)	26/113 (23.0)	.81
ICA			
Extracranial	10/138 (7.2)	20/113 (17.7)	NA
Intracranial	13/138 (9.4)	9/113 (7.9)	NA
M1 MCA	81/138 (58.7)	40/113 (35.4)	NA
M2 MCA	35/138 (25.4)	45/113 (39.8)	NA
Occlusion			
Proximal[b]	104/138 (75.3)	68/113 (60.2)	.01
Tandem	5/138 (3.6)	1/113 (0.9)	.16

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CS, collateral score; CTA, computed tomography angiography; DBP, diastolic blood pressure; ELVO, emergency large-vessel occlusion; ICA, internal carotid artery; IQR, interquartile range; IVtPA, intravenous tissue plasminogen activator; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; tPA, tissue plasminogen activator.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] Collateral score for anterior circulation ELVO was reported in a dichotomized fashion (ie, poor [CS = 0 or 1] vs good [CS = 2, 3, and 4]) using American Society of Interventional and Therapeutic Neuroradiology methods that have been shown to predict outcomes.[20]

[b] Internal carotid artery, M1 middle cerebral artery.

and 22% (n = 25 of 113) of the MT and bMM groups. After dichotomizing baseline characteristics and outcomes according to the patient enrollment period (until June 2015 vs following June 2015), no significant differences were evident in patients recruited before the publication of MT trials (January 2013 to June 2015) and those recruited after July 2015 (eTable 2 in the Supplement).

In multivariable analyses after adjustment for potential confounders (**Table 3**), MT was associated with higher odds of asymptomatic ICH (OR, 11.07; 95% CI, 1.31-93.53; *P* = .03). There was no association of treatment modality with the likelihood of sICH (OR, 2.09; 95% CI, 0.16-27.85; *P* = .58), FFO (OR, 0.72; 95% CI, 0.31-1.72; *P* = .47), FI (OR, 0.73; 95% CI, 0.19-2.75; *P* = .64), functional improvement (common OR, 0.72; 95% CI, 0.32-1.64; *P* = .43), or mortality (OR, 1.79; 95% CI, 0.62-5.23, *P* = .28) at 3 months after including patients with missing 3-month follow-up using LOCF methods on multivariable ordinal logistic regression analyses.

In multivariable analyses using as confounders baseline characteristics contributing to the outcome of interest in the initial univariable analyses at *P* values less than .10, MT was associated with higher odds of asymptomatic ICH (OR, 4.13; 95% CI, 1.50-11.40; *P* = .006; eTable 3 in the Supplement) and lower likelihood of 3-month FI in patients receiving treatment with MT after including patients with missing 3-month follow-up using LOCF methodology (OR, 0.42; 95% CI, 0.18-0.96; *P* = .04; eTable 4 in the Supplement). Again, no association of treatment modality with functional improvement at 3 months was seen after including patients with missing 3-month follow-up using LOCF methods (common OR, 0.79; 95% CI, 0.51-1.25; *P* = .31; eTable 5 in the Supplement) on multivariable ordinal logistic regression analyses.

Table 2. Safety and Efficacy Outcomes in Patients Treated With Mechanical Thrombectomy and Best Medical Management

Outcome	Median (IQR)		P Value
	Mechanical Thrombectomy (n = 138)	Best Medical Management (n = 113)	
Length of stay, d			
Hospital	5 (4-9)	4 (3-7)	.002
ICU	2 (1-4)	3 (1-4)	.38
Successful reperfusion, No./total No. (%)	117/138 (84.5)	NA	NA
ICH, No./total No. (%)			
Asymptomatic	31/137 (22.3)	4/109 (3.2)	.002
Symptomatic	6/137 (4.4)	1/107 (0.9)	.11
Discharge NIHSS	2 (0-4)	1 (0-2)	.02
Neurological improvement during hospitalization[a]	2 (1-3)	1 (0-3)	.69
Discharge mRS	1 (1-3)	1 (0-2)	.002
3-mo Follow-up			
mRS	1 (0-2)	1 (0-2)	.09
FFO, No./total No. (%)	84/133 (63.1)	62/88 (70.4)	.26
FI, No./total No. (%)	102/133 (76.7)	75/88 (85.2)	.12
Mortality, No./total No. (%)	13/133 (9.7)	5/88 (5.7)	.28
With LOCF			
mRS	1 (0-2)	1 (0-2)	.06
FFO, No./total No. (%)	88/138 (63.7)	81/113 (71.6)	.17
FI, No./total No. (%)	106/138 (76.8)	100/113 (88.4)	.02
Mortality, No./total No. (%)	13/138 (9.4)	4/113 (3.5)	.12

Abbreviations: FFO, favorable functional outcome; FI, functional independence; ICH, intracranial hemorrhage; ICU, intensive care unit; IQR, interquartile range; LOCF, last observation carried forward; mRS, modified Rankin Scale score; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

[a] Defined as the decrease in the baseline NIHSS score at hospital discharge (baseline NIHSS score minus discharge NIHSS score).

Table 3. Overview of Primary and Secondary Analyses Evaluating the Association of Treatment Modality (Mechanical Thrombectomy vs Best Medical Management) With Safety and Efficacy Outcomes in the Study Cohort

Outcome	Type of Analysis	Unadjusted Analyses		Adjusted Analyses[a,b]	
		OR (95% CI)	P Value	aOR (95% CI)	P Value
3-mo FFO	Without LOCF	0.72 (0.40-1.28)	.26	0.60 (0.22-1.64)	.32
	With LOCF	0.69 (0.40-1.18)	.17	0.72 (0.31-1.72)	.47
3-mo FI	Without LOCF	0.57 (0.28-1.16)	.12	0.73 (0.19-2.75)	.64
	With LOCF	0.44 (0.22-0.90)	.02	0.47 (0.14-1.64)	.24
3-mo Mortality	Without LOCF	1.62 (0.20-12.93)	.65	1.79 (0.62-5.23)	.28
	With LOCF	2.26 (0.78-6.56)	.13	1.73 (0.21-13.87)	.61
Functional improvement	Without LOCF	0.68 (0.42-1.12)	.13	0.72 (0.32-1.64)	.43
	With LOCF	0.79 (0.50-1.25)	.31	0.81 (0.39-1.67)	.56
Symptomatic ICH	NA	4.85 (0.57-40.95)	.15	2.09 (0.16-27.85)	.58
Asymptomatic ICH	NA	4.42 (1.62-12.00)	.004	11.07 (1.31-93.53)	.03

Abbreviations: aOR, adjusted odds ratio; FFO, favorable functional outcome; FI, functional independence; ICH, intracranial hemorrhage; LOCF, last observation carried forward; NA, not applicable; OR, odds ratio.

[a] Adjusted for a priori–defined confounders: age, National Institutes of Health Stroke Scale and collateral status, and Alberta Stroke Program Early CT Score on baseline neuroimaging, history of disability prior to current event, and treatment with mechanical thrombectomy.

[b] Adjusted for a priori–defined confounders: age, National Institutes of Health Stroke Scale and collateral status, and Alberta Stroke Program Early CT Score on baseline neuroimaging, admission glucose level, and treatment with mechanical thrombectomy.

Propensity score matching resulted in groups balanced for all baseline characteristics (eTable 6 in the Supplement). In propensity score–matched sensitivity analyses, patients receiving MT (n = 94) had more prolonged hospital stay (5 days; interquartile range, 4-9 vs 4 days; interquartile range, 3-7, $P = .005$) and higher rates of asymptomatic ICH (22.6% [n = 21 of 94] vs 3.3% [n = 3 of 94]; $P < .001$) compared with their bMM matched counterparts (n = 94). The 2 groups did not differ in any other safety or efficacy outcome.

Subgroup Analyses

We further performed additional subgroup analyses according to location of occlusion (proximal [ICA and M1 MCA] vs distal [M2 MCA]; eTable 7 in the Supplement) and stroke severity on admission (NIHSS scores 0-3 vs NIHSS scores 4-5, eTable 8 in the Supplement). The 2 groups had similar functional outcomes in these subgroup analyses. Patients treated with MT had higher asymptomatic ICH rates in the following subgroups: proximal intracranial occlusions (16.5% [n = 28 of

Table 4. Baseline Characteristics of Studies in Systematic Review and Meta-analysis

Source	Study Type	No. of Patients	MT, No./ Total No. (%)	Age, Mean (SD)	Male, No./ Total No. (%)	Occlusion Site (%)	IVT, No./ Total No. (%)	Rescue MT, No./ Total No. (%)	Confounder Adjustment
Goyal et al,[19] 2019	Multicenter	251	138/251 (55.0)	65 (15)	133/251 (52.9)	ICA: 17.8; M1-MCA: 48.0; M2-MCA: 31.7	121/249 (48.6)	NA	Multivariable regression
Nagel et al,[25] 2018	Multicenter	300	81/300 (27)	68 (14)	162/300 (54)	ICA: 9; tandem: 12; M1-MCA: 27.1; M2-MCA: 43.8; ACA: 3; BA: 21	152/300 (50.7)	34/300 (11.3)	PSM
Sarraj et al,[16] 2018	Multicenter	214	124/214 (57.9)	65 (16)	124/214 (57.9)	ICA: 15.4; MCA-M1: 41.6; MCA-M2: 36; MCA-M3/M4 & ACA: 6.9	69/214 (32.2)	NA	Multivariable regression
Urra et al,[14] 2014	Multicenter	78	34/78 (43.6)	67.9	39/78 (50.0)	ICA: 1.3; MCA-M1: 33.3; MCA-M2: 29.5; tandem: 5.1; posterior: 30.8	45/78 (57.7)	16/78 (20.5)	NA

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; MT, mechanical thrombectomy; NA, not available; PSM, propensity score matching.

Table 5. Overview of Primary and Secondary Analyses Evaluating the Association of Treatment Modality (Mechanical Thrombectomy vs Best Medical Management) With Safety and Efficacy Outcomes in the Systematic Review and Meta-analysis

		Unadjusted Analyses					Adjusted Analyses				
					Heterogeneity					Heterogeneity	
Outcome	Type of Analysis	No. of Studies	OR (95% CI)	*P* Value	I^2, %	*P* Value for Cochran Q	No. of Studies	OR (95% CI)	*P* Value	I^2, %	*P* Value for Cochran Q
3-mo FFO	Without LOCF	4	0.96 (0.71-1.30)	.78	0	.48	3	1.13 (0.78-1.65)	.51	0	.51
	With LOCF	4	0.93 (0.69-1.26)	.65	0	.40	3	1.09 (0.76-1.57)	.65	0	.39
3-mo FI	Without LOCF	4	0.94 (0.48-1.86)	.86	71	.02	3	1.11 (0.55-2.27)	.77	62	.07
	With LOCF	4	0.88 (0.41-1.87)	.74	76	.005	3	0.96 (0.38-2.46)	.94	77	.01
3-mo Mortality	Without LOCF	4	1.71 (0.52-5.61)	.38	62	.05	2	1.28 (0.51-3.23)	.60	0	.38
	With LOCF	4	1.85 (0.54-6.28)	.32	64	.04	2	1.45 (0.52-4.07)	.48	20	.26
sICH	NA	4	5.52 (1.91-15.94)	.002	0	.83	2	2.89 (0.75-11.20)	.12	0	.53
Asymptomatic ICH	NA	2	1.85 (0.34-10.13)	.48	84	.01	1	NA	NA	NA	NA

Abbreviations: FFO, favorable functional outcome; FI, functional independence; ICH, intracranial hemorrhage; LOCF, last observation carried forward; NA, not applicable; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

173] vs 4.6% [n = 8 of 173]), distal intracranial occlusions (20.5% [n = 16 of 78] vs 5.1% [n = 4 of 78]), and admission NIHSS scores of 4 to 5 (18.6% [n = 25 of 134] vs 4.5% [n = 6 of 134]).

Systematic Review and Meta-analysis

For meta-analysis, the search of MEDLINE and SCOPUS databases yielded 414 and 154 results, respectively. After removing duplicates, the titles and abstracts from the remaining 508 studies were screened, and 7 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 7 studies, 4 studies were excluded because they reported data that were already published in previous studies (overlapping data) or used a different cutoff for defining mild stroke severity (eTable 9 in the Supplement).

A total of 4 studies (including this study) met the inclusion criteria[14,16,25] and were included in our meta-analysis (eFigure 1 in the Supplement). The risks of bias of included studies are summarized in eTable 10 in the Supplement. The individual characteristics of the included studies are shown in **Table 4**, while the results of the meta-analysis are briefly summarized in **Table 5**. The pooled risk of bias was low, with a total score of 33 of 36 in Newcastle-Ottawa Scale.

In unadjusted analyses (eFigures 2-7 in the Supplement; Table 5), there was no association between treatment modality and asymptomatic ICH (4 studies; OR, 1.85; 95% CI, 0.34-10.13; *P* = .48), 3-month FFO (4 studies; OR, 0.96; 95% CI, 0.71-1.30; *P* = .78), 3-month FI (4 studies; OR, 0.94; 95% CI, 0.48-1.86; *P* = .86), and 3-month mortality (OR, 1.71; 95% CI, 0.52-5.61; *P* = .38). There was no heterogeneity noted for 3-month FFO (I^2 = 0%; *P* for Cochran Q = .48); however, substantial heterogeneity was observed for asymptomatic ICH (I^2 = 84%; *P* for Cochran Q = .01), 3-month FI (I^2 = 71%; *P* for Cochran Q = .02), and 3-month mortality (I^2 = 62%; *P* for Cochran Q = .05). Mechanical thrombectomy was associated with higher odds of sICH (4 studies; OR, 5.52; 95% CI, 1.91-15.49; *P* = .002) in unadjusted analyses without an evidence of heterogeneity (I^2 = 0%; *P* for Cochran Q = .83). We detected no association between treatment modality and 3-month FFO (3 studies; OR, 1.16; 95% CI, 0.75-1.79); 3-month FI (3 studies; OR, 1.24; 95% CI, 0.61-2.53); 3-month mortality (2 studies; OR, 1.34; 95% CI, 0.56-3.22); and sICH (2 studies; OR, 2.06; 95% CI, 0.49-8.63) in adjusted analyses (eFigures 8-11 in the Supplement).

Discussion

Our multicenter study coupled with a comprehensive meta-analysis demonstrates similar efficacy profile for MT and

bMM in patients with AIS with mELVO. In terms of safety, our multicenter study documents an increased risk of asymptomatic ICH with MT, even after adjustment of potential confounders. In terms of efficacy, MT was associated with lower odds of 3-month FI in multivariable models adjusting for confounders after imputation of missing follow-up data, but this association was not detected in the analysis that excluded patients with missing 3-month follow-up evaluations. Moreover, our meta-analysis failed to detect an independent association between treatment modality and asymptomatic ICH. Notably, we documented an independent association of MT with higher odds of sICH in unadjusted analyses of 4 available reports, but this association did not retain its statistical significance in adjusted analyses of 2 available studies.

Our findings support a 2018 study conducted by Sarraj et al[16] that reported no difference in clinical outcomes in patients with mELVO treated with MT or bMM. However, in contrast to their study that additionally included M3 and M4 occlusions, we restricted enrollment of patients with mELVO to location of occlusion involving ICA, M1, and M2. In another multicenter study[14] comparing MT and bMM in patients with mELVO, the investigators reported higher rates of sICH in MT but similar clinical outcomes between the 2 groups. These observations also corroborate our study findings. Similarly, another multicenter study[15] failed to document any differences in clinical outcomes between urgent MT and bMM combined with rescue MT in patients with potential clinical worsening. Contrary to our and the aforementioned[14-16] observations, analyses from Grady Endovascular Stroke Outcomes Registry (GESTOR) and Screening Technology and Outcomes Project in Stroke (STOPstroke) databases demonstrated increased rates of 3-month FI[10]; however, the study sample size was small and included only 30 patients in the MT arm. Additionally, the medical arm comprised all consecutive patients from 2003 to 2005 and may not be reflective of bMM in the current era.

Our study represents, to our knowledge, the largest meta-analysis on this topic to date. Contrary to our findings, a prior meta-analysis by Xiong et al[26] showed that patients with ELVO with minor or mild symptoms (NIHSS ≤8) who underwent MT had a significantly better 90-day mRS score at the cost of higher rate of sICH compared with those who received bMM. Apart from the larger sample size of our meta-analysis, important methodologic differences existed in comparison with the meta-analysis by Xiong et al.[26] We included studies with mild strokes as NIHSS of 5 or less rather than Xiong et al,[26] who included studies with mild strokes as NIHSS ≤8.

Our study involves more patients with proximal intracranial (internal carotid artery and M1 middle cerebral artery) occlusions in the MT group, as did the study by Sarraj et al.[16] Theoretically, proximal anterior circulation occlusions might predispose patients to a higher risk of worsening. This might lead clinicians to offer MT to these patients with ELVO despite low NIHSS scores at hospital admission. The lack of improved clinical outcomes in the MT group is consequently counterintuitive and may be attributed to intrinsic ischemic preconditioning in patients with mELVO owing to good collateral status (81% in our multicenter cohort [n = 80 of 99]). Notably, Dargazanli et al[15] reported that more than 80% of patients in the bMM group did not experience clinical worsening and only 18% of patients required rescue MT because of neurological worsening. An alternative explanation may be that the ischemic territory at risk in patients with mELVO may be restricted to a small cerebral area, negating the potential beneficial effect of endovascular reperfusion. The interpatient variation in the topographic distributions of major cerebral arteries influenced by leptomeningeal collaterals argues in favor of this hypothesis.[27] Thus, the optimal selection of patients with mELVO for MT may require advanced neuroimaging to determine whether certain perfusion or collateral thresholds predict neurologic deterioration.

Strengths and Limitations

The main strengths of our study are related to the evaluation of a large multicenter cohort derived from real-world daily practice in different countries in North America, Europe, and Asia. We also conducted an updated meta-analysis in an attempt to pool our findings with other similar studies that evaluated MT vs bMM in patients with ELVO with mild neurological deficits using identical NIHSS score cutoff (<6 points). On the other hand, some limitations of our work must be acknowledged. First, it is a retrospective study: the lack of randomization and potential residual confounding are important considerations when interpreting the results of our study. Furthermore, it should be highlighted that our study had a limited sample size, and therefore, the fact that we failed to identify independent associations between treatment modality (MT vs bMM) and outcomes may be attributed to the low statistical power. For instance, the difference in sICH rates between the 2 groups was not significant owing to the limited sample size (n = 251) and not treatment effect (4.4% in MT vs 0.9% in bMM) because the sICH rate in the MT group was not negligible (4.4%) in a stroke population with minor stroke (admission NIHSS scores of 0-5 points). Second, the specific devices and reperfusion approaches used during MT were heterogeneous and were selected according to the treating physicians' preference. Third, the safety and efficacy outcomes in different centers were self-reported and lack central adjudication. Fourth, patients undergoing MT tended to have more severe strokes and were more likely to have proximal occlusions. However, both of these variables were included and adjusted in the multivariable models of different outcomes measures. Fifth, we used mRS score as an outcome measure of functional outcome that may not be adequate to assess small improvements in hand or language functions in patients with mELVO. We propose that future studies evaluating clinical outcomes in patients with mELVO treated with MT vs bMM should use the Barthel Index as a standard outcome measure of activities of daily living at 3 months. Six, the NIHSS may not be adequate to access severity of minor strokes on admission. For example, NIHSS of 3 or 4 with deficits of hemianopia or aphasia would be significantly disabling, and MT may be offered. However, the MT may not be offered for the same patient with the same NIHSS who has mild facial droop, very mild hemiparesis, and minimal dysarthria. In

this study, we do not have data available regarding type of initial deficit. Future studies evaluating safety and efficacy of MT in minor strokes should obtain data regarding type of initial deficits and correlate those with outcomes. We attempted to address some of these methodologic shortcomings by performing rigorous multivariable analyses adjusting for several potential confounders; however, clinical equipoise regarding the comparative safety and efficacy of MT and bMM in patients with mELVO can only be resolved by a randomized clinical trial.

Conclusions

In conclusion, our multicenter study coupled with a comprehensive meta-analysis documented similar outcomes between MT and bMM in patients with AIS with mELVO, but no conclusions about treatment effect can be made. Future randomized clinical trials are required to definitely evaluate the potential efficacy of MT compared with bMM in patients with ELVO presenting with mild neurological deficits.

ARTICLE INFORMATION

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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018;49(3):e46-e110. doi:10.1161/STR.0000000000000158

2. Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061

3. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030. doi:10.1056/NEJMoa1414905

4. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306. doi:10.1056/NEJMoa1503780

5. Albers GW, Marks MP, Kemp S, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973

6. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587

7. Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018. doi:10.1056/NEJMoa1414792

8. Maas MB, Furie KL, Lev MH, et al. National Institutes of Health Stroke Scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. *Stroke*. 2009;40(9):2988-2993. doi:10.1161/STROKEAHA.109.555664

9. Heldner MR, Jung S, Zubler C, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. *J Neurol Neurosurg Psychiatry*. 2015;86(7):755-760. doi:10.1136/jnnp-2014-308401

10. Haussen DC, Bouslama M, Grossberg JA, et al. Too good to intervene? thrombectomy for large vessel occlusion strokes with minimal symptoms: an intention-to-treat analysis. *J Neurointerv Surg*. 2017;9(10):917-921. doi:10.1136/neurintsurg-2016-012633

11. Heldner MR, Zubler C, Mattle HP, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke*. 2013;44(4):1153-1157. doi:10.1161/STROKEAHA.111.000604

12. Mokin M, Masud MW, Dumont TM, et al. Outcomes in patients with acute ischemic stroke from proximal intracranial vessel occlusion and NIHSS score below 8. *J Neurointerv Surg*. 2014;6(6):413-417. doi:10.1136/neurintsurg-2013-010720

13. Haussen DC, Lima FO, Bouslama M, et al. Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: an analysis from STOPStroke and GESTOR cohorts. *J Neurointerv Surg*. 2018;10(4):325-329. doi:10.1136/neurintsurg-2017-013243

14. Urra X, San Román L, Gil F, et al; Catalan Stroke Code and Reperfusion Consortium (Cat-SCR). Medical and endovascular treatment of patients with large vessel occlusion presenting with mild symptoms: an observational multicenter study. *Cerebrovasc Dis*. 2014;38(6):418-424. doi:10.1159/000369121

15. Dargazanli C, Arquizan C, Gory B, et al; ETIS REGISTRY Investigators. Mechanical thrombectomy for minor and mild stroke patients harboring large vessel occlusion in the anterior circulation: a multicenter cohort study. *Stroke*. 2017;48(12):3274-3281. doi:10.1161/STROKEAHA.117.018113

16. Sarraj A, Hassan A, Savitz SI, et al. Endovascular thrombectomy for mild strokes: how low should we go? *Stroke*. 2018;49(10):2398-2405. doi:10.1161/STROKEAHA.118.022114

17. Goyal N, Tsivgoulis G, Frei D, et al. A multicenter study of the safety and effectiveness of mechanical thrombectomy for patients with acute ischemic stroke not meeting top-tier evidence criteria. *J Neurointerv Surg*. 2018;10(1):10-16. doi:10.1136/neurintsurg-2016-012905

18. Goyal N, Tsivgoulis G, Frei D, et al. Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion. *Neurology*. 2018;90(15):e1274-e1282. doi:10.1212/WNL.0000000000005299

19. Goyal N, Tsivgoulis G, Frei D, et al. Comparative safety and efficacy of modified TICI 2b and TICI 3 reperfusion in acute ischemic strokes treated with mechanical thrombectomy. *Neurosurgery*. 2019;84(3):680-686. doi:10.1093/neuros/nyy097

20. Liebeskind DS, Tomsick TA, Foster LD, et al; IMS III Investigators. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke*. 2014;45(3):759-764. doi:10.1161/STROKEAHA.113.004072

21. Knobloch K, Yoon U, Vogt PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. *J Craniomaxillofac Surg*. 2011;39(2):91-92. doi:10.1016/j.jcms.2010.11.001

22. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

23. Malhotra K, Ahmed N, Filippatou A, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Stroke*. 2019;21(1):78-90. doi:10.5853/jos.2018.02369

24. George BJ, Aban IB. An application of meta-analysis based on DerSimonian and Laird method. *J Nucl Cardiol*. 2016;23(4):690-692. doi:10.1007/s12350-015-0249-6

25. Nagel S, Bouslama M, Krause LU, et al. Mechanical thrombectomy in patients with milder strokes and large vessel occlusions. *Stroke*. 2018;49(10):2391-2397. doi:10.1161/STROKEAHA.118.021106

26. Xiong YJ, Gong JM, Zhang YC, et al. Endovascular thrombectomy versus medical treatment for large vessel occlusion stroke with mild symptoms: a meta-analysis. *PLoS One*. 2018;13(8):e0203066. doi:10.1371/journal.pone.0203066

27. Cheng B, Golsari A, Fiehler J, Rosenkranz M, Gerloff C, Thomalla G. Dynamics of regional distribution of ischemic lesions in middle cerebral artery trunk occlusion relates to collateral circulation. *J Cereb Blood Flow Metab*. 2011;31(1):36-40. doi:10.1038/jcbfm.2010.185