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First pass effect as an independent predictor of functional outcomes in medium vessel occlusions: An analysis of an international multicenter study

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Abstract

Introduction: First pass effect (FPE), achievement of complete recanalization (mTICI 2c/3) with a single pass, is a significant predictor of favorable outcomes for endovascular treatment (EVT) in large vessel occlusion stroke (LVO). However, data concerning the impact on functional outcomes and predictors of FPE in medium vessel occlusions (MeVO) are scarce.

Patients and Methods: We conducted an international retrospective study on MeVO cases. Multivariable logistic modeling was used to establish independent predictors of FPE. Clinical and safety outcomes were compared between the two study groups (FPE vs non-FPE) using logistic regression models. Good outcome was defined as modified Rankin Scale 0–2 at 3 months.

Results: Eight hundred thirty-six patients with a final mTICI ⩾ 2b were included in this analysis. FPE was observed in 302 patients (36.1%). In multivariable analysis, hypertension (aOR 1.55, 95% CI 1.10–2.20) and lower baseline NIHSS score (aOR 0.95, 95% CI 0.93–0.97) were independently associated with an FPE. Good outcomes were more common in the FPE versus non-FPE group (72.8% vs 52.8%), and FPE was independently associated with favorable outcome (aOR 2.20, 95% CI 1.59–3.05). 90-day mortality and intracranial hemorrhage (ICH) were significantly lower in the FPE group, 0.43 (95% CI, 0.25–0.72) and 0.55 (95% CI, 0.39–0.77), respectively.
Conclusion: Over 2/3 of patients with MeVOs and FPE in our cohort had a favorable outcome at 90 days. FPE is independently associated with favorable outcomes, it may reduce the risk of any intracranial hemorrhage, and 3-month mortality.

Keywords
Stroke, thrombectomy, outcomes research, MeVO, reperfusion

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Background

First-pass effect (FPE) is a major predictor of favorable outcomes following endovascular treatment (EVT) for large vessel occlusion (LVO) stroke.[1–3] In LVO stroke, the proportion of patients who achieve FPE ranges from 19% to 58%, and factors influencing FPE may include age, female sex, diabetes mellitus, underlying stroke etiology, general anesthesia, first-line EVT approach (direct aspiration first pass technique (ADAPT) or stent-retriever thrombectomy (SR) or combined), use of balloon guide, and occlusion location.[4,5] Presumably, the impact of FPE is similar for medium vessel occlusions (MeVOs) as it would be for LVOs. However, this has not been established, and the association's strength may differ between occlusion locations. These more distal occlusions were underrepresented or excluded in the pivotal thrombectomy trials, and observational data are limited.

A small retrospective study reported an FPE rate of 32% in MeVO, associated with a higher likelihood of favorable clinical outcomes.[6] This is similar to FPE rates observed in the LVO trials.[7] Several other retrospective studies and meta-analyses have identified FPE rates of up to 50% in distal and middle vessel occlusions (DMVO).[8] However, most of the studies in this meta-analysis focused on M2 occlusions, for which the FPE is higher.[4,8]

MeVOs are associated with lower stroke severity and better outcome than LVOs.[9] Moreover, with tissue plasminogen activator (tPA) treatment alone, up to 50% of the patients achieve an excellent outcome, and 67.4% gain functional independence, while up to 65.3% achieve functional independence without reperfusion treatment.[10] Given the relatively favorable natural history of MeVO, it is important to reduce complications, determine predictors of good clinical outcomes, and determine the ideal techniques to achieve them. Therefore, we explored the prognostic value of FPE, and the factors associated with it in patients with MeVOs using a large multicenter registry.

Methods

Patient population

The Multicenter Analysis of primary Distal medium vessel occlusions: effect of Mechanical Thrombectomy (MAD-MT) registry collected data from 37 sites in 11 countries (Austria, Belgium, Canada, France, Germany, Japan, Italy, Portugal, Singapore, Taiwan, and the United States). All data were collected from the centers for patients with acute ischemic stroke who underwent thrombectomy for primary medium-proximal (M2, A1, P1) or primary medium distal vessel (M3, A2, P2, and further) occlusions between September 2016 – December 2021 and no core-lab adjudication was available. The detailed inclusion protocol was previously reported.[11]

This secondary analysis included patients with complete data regarding key clinical characteristics: baseline National Institute of Health Stroke Scale (NIHSS), final thrombolysis in cerebral infarction score (mTICI), and the number of passes. FPE was defined as mTICI 2c/3 in one pass. We excluded patients: (1) for which thrombectomy was not performed (treated medically or with intra-arterial tPA); (2) patients with a final mTICI score of 2a or less; (3) patients with missing potential confounding factors (occlusion type, patient age, pre-stroke mRS, puncture to recanalization delay, baseline imaging data).[12] Our primary analysis compared patients with FPE with recanalized patients mTICI 2b/3. To analyze the effect of complete or near-complete recanalization in one single pass versus recanalization in multiple passes on the outcome, and not the impact of recanalization itself, we performed a secondary analysis comparing FPE with recanalized patients mTICI 2c/3 (see Supplemental Table 1 and 2).

Excellent outcome was described as an mRS 0–1 or equal to pre-stroke mRS, and good outcome as mRS 0–2 or equal to pre-stroke mRS at 3 months. Symptomatic intracranial hemorrhage (sICH) was determined based on ECASS 2 criteria.[13]

Our analysis aimed to define the impact of FPE on clinical and safety outcomes and to identify potential predictors of FPE. The primary endpoint was 90-day good outcome (mRS 0–2). Secondary endpoints were excellent 90-day outcome, mean change in NIHSS at 24 h, and mortality at 3 months. The safety outcomes were any investigated separately as: any intracranial hemorrhage, parenchymal hemorrhage (PH), subarachnoid hemorrhage (SAH), sICH, and procedural complications.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Normality of distributions was assessed graphically and by using the Shapiro-Wilk test. Quantitative variables were expressed as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate.

Associations of baseline characteristics (patient's and treatment characteristics) with FPE were first investigated by using Student t test (or Mann-Whitney *U* test in case of deviation to non-normal distributions) for continuous variables or using Chi-Square test (or Fisher's exact tests when expected cell frequency <5) for categorical variables. To assess the independent predictors of FPE, all patients' and treatment characteristics with a $p < 0.10$ in bivariate analyses were entered into a backward-stepwise multivariable logistic model using a removal criteria of $p > 0.05$. Adjusted odds ratios (aORs) were calculated as effect size using non FPE group as reference. Before developing the multivariable prognostic model, we examined the log-linearity

assumption for continuous characteristics using restricted cubic spline functions,[14] and the presence of collinearity between candidate predictors by calculating the variance inflation factors (VIFs).[15] We examined the performance of the selected model in terms of discrimination by calculating the c-statistics.[14]

Comparisons in binary outcomes (favorable and excellent outcome, 90-day all-cause mortality, procedural and intracranial hemorrhagic complications) between the two study groups (FPE vs non-FPE) were also performed using logistic regression models; odds ratios (ORs) were calculated as effect size using non-FPE group as reference. Comparison in the overall distribution of mRS was performed using an ordinal logistic regression model (shift analysis) including FPE group as covariate; common odds ratio for 1 point improvement in mRS was derived from this model as effect size using non FPE group as reference. Comparison in 24-h change in NIHSS was performed using a linear model that included FPE group and admission NIHSS score as covariates; the mean between-group difference (FPE vs non-FPE group) was derived from this model as effect size. Normality of model residuals was checked and satisfied. Comparisons in outcomes were further adjusted for independent predictors of FPE.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

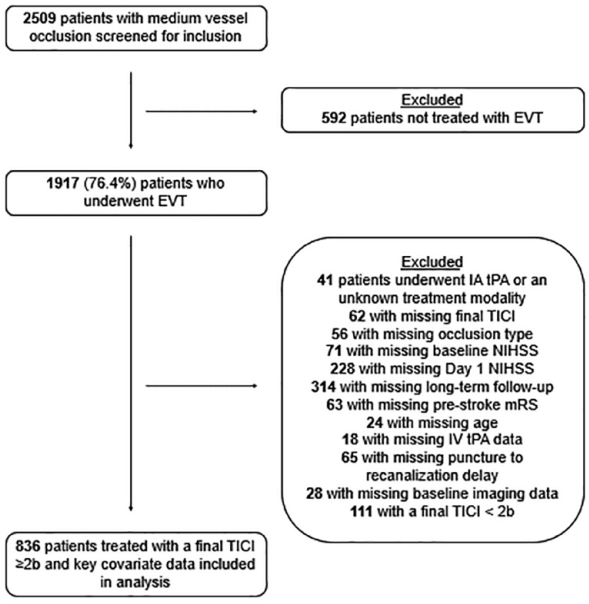

Figure 1. Inclusion flowchart.
EVT: endovascular thrombectomy; IA tPA: intraarterial tissue plasminogen activator; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; mTICI: thrombolysis in cerebral infarction score.

Results

A total of 2509 patients were recruited in the MAD-MT registry. Among them, 836 patients with medium vessel occlusions were treated with thrombectomy and achieved successful reperfusion (final mTICI ⩾ 2b), allowing inclusion in the present study (Figure 1). The patient and treatment characteristics in the study groups are reported in Table 1. Overall, the mean age was 72.3 years (SD, 13.6), 50.4% ($n=421$) were women, and the median admission NIHSS score was 10 (IQR, 6–16). Hypertension occurred in 76% of the population ($n=635$), and 76.2% had a pre-stroke mRS of 0–1 ($n=596$). The median time from onset to puncture was 246 min (IQR, 165–420 min), and 32.2% of patients underwent general anesthesia ($n=267$). After a first pass of the device, near to complete recanalization (mTICI 2c/3, defined as FPE) was achieved in 302 patients (36.1%; 95% CI, 32.9–39.5%). In the non FPE group, the median number of passes was 2 (25%–75% IQR 2–3). Fifty-two percent of the cases obtained a final mTICI of 2b, 30% a final mTICI of 3.

Predictors of first pass effect

Bivariate associations of FPE with patients and treatment characteristics are detailed in Table 1. Factors entered in the multivariable analysis were hyperlipidemia, hypertension, and baseline NIHSS. In a multivariable analysis, hypertension (aOR = 1.55, 95% CI 1.10–2.20, $p=0.013$) and baseline NIHSS score (per one point increase, aOR = 0.95, 95% CI 0.93–0.97, $p<0.001$) were independently associated with an FPE. This selected model had a good discrimination (c-statistic 0.59).

Efficacy outcomes and first pass effect

Favorable and excellent outcomes were more often observed when FPE was achieved (72.8% vs 52.8% and 53.6% vs 34.1% in patients without FPE, respectively). These differences were still significant after further adjustment on predictors of FPE (high blood pressure and NIHSS baseline score) (aOR = 2.20, 95% CI 1.59–3.05 for favorable outcome and aOR = 2.03, 95% CI 1.49–2.77 for excellent outcome) (Table 2). On ordinal regression, FPE was associated with a shift toward lower mRS scores (Figure 2, OR, 2.05; 95% CI 1.58–2.65). Regarding the change in NIHSS score at 24 h, FPE was associated with a significantly greater decrease in NIHSS, with a fully adjusted mean difference of 2.88 points (95% CI, 1.86–3.90) in favor of the FPE group.

Safety outcomes and first pass effect

Ninety-day all-cause mortality and any ICH were significantly lower in the case of FPE both in bivariate and fully adjusted analyses (Table 2). The fully adjusted OR associated with FPE was 0.43 (95% CI, 0.25–0.72) for all-cause mortality, and 0.55 (95% CI, 0.39–0.77) for any ICH.

Table 1. General characteristics of patients according to first pass effect.

Predictors	All ($n=836$)	FPE (−) ($n=534$)	FPE (+) ($n=302$)	p-Value
Age, years	72.3 (13.6)	72.2 (13.5)	72.4 (13.8)	0.85
Female	421/836 (50.4)	267/534 (50.0)	154/302 (51.0)	0.78
Medical history				
Hypertension	635/836 (76.0)	393/534 (73.6)	242/302 (80.1)	0.034
Diabetes	199/836 (23.8)	124/534 (23.2)	75/302 (24.8)	0.60
Hyperlipidemia	318/836 (38.0)	192/534 (36.0)	126/302 (41.7)	0.099
Weight (kg)	79.2 (19.1)	78.8 (18.2)	79.7 (20.3)	0.71
Pre-stroke antiplatelets	255/765 (33.3)	166/486 (34.2)	89/279 (31.9)	0.52
Pre-stroke anticoagulants	191/728 (26.2)	123/464 (26.5)	68/264 (25.8)	0.82
Current smoking	104/836 (12.4)	68/534 (12.7)	36/302 (11.9)	
Pre-stroke mRS of 0–1	596/782 (76.2)	384/502 (76.5)	212/280 (75.7)	0.81
Atrial fibrillation	326/836 (39.0)	204/534 (38.2)	122/302 (40.4)	0.53
Clinical presentation				
Heart rate (bpm), median (IQR)	79 (69–92)	80 (69–93)	78 (68–90)	0.88
Systolic blood pressure (mmHg)	153 (29.8)	154 (29.1)	151 (31.0)	0.43
Diastolic blood pressure (mmHg)	88.4 (55.3)	90.4 (67.9)	85.1 (18.0)	0.24
Temperature (°C)	36.7 (3.5)	36.5 (0.7)	37.0 (5.6)	0.27
Baseline NIHSS, median (IQR)	10 (6–16)	12 (6–17)	9 (5–14)	<0.001
IVtPA	410/826 (49.6)	263/529 (49.7)	147/297 (49.5)	0.95
Glucose (mg/dl), median (IQR)	117 (102–141)	116 (102–141)	117 (103–141)	0.69
Mechanical thrombectomy				
Admission mothership	460/789 (58.3)	299/507 (59.0)	161/282 (57.1)	0.61
General anesthesia	267/829 (32.2)	173/531 (32.6)	94/298 (31.5)	0.76
First line – technique				
Contact aspiration	163/835 (19.5)	95/533 (17.8)	68/302 (22.5)	0.16
Stent-retriever	108/835 (12.9)	75/533 (14.1)	33/302 (10.9)	
Combined	564/835 (67.5)	363/533 (68.1)	201/302 (66.6)	
Balloon guide catheter	134/379 (35.5)	77/235 (32.7)	57/144 (39.5)	0.17
Times				
Onset to puncture delay in min, median (IQR)	242 (165–420)	240 (170–407)	242 (160–425)	0.66
Unknown onset (%)	287/782 (36.7)	172/493 (34.9)	115/289 (39.8)	0.17
Imaging				
Initial occlusion				
A1-2-3	35/836 (4.2)	24/534 (4.5)	11/302 (3.6)	0.63
P1-2-3	49/836 (5.9)	33/534 (6.2)	16/302 (5.3)	
M2	637/836 (76.2)	409/534 (76.6)	228/302 (75.5)	
M3–4	115/836 (13.8)	68/534 (12.7)	47/302 (15.6)	
Left side (%)	410/830 (49.4)	261/530 (49.2)	149/300 (49.7)	0.91

FPE: first pass effect; mRS: modified rankin scale; NIHSS: National Institutes of Health Stroke Scale.
Values are expressed as number (percentage) or mean (SD) unless otherwise indicated. p-Values calculated using Chi-square test, student t test or Wilcoxon test according factors.

PH, SAH, and procedural complications were significantly reduced with FPE in bivariate analyses (all p-values < 0.004), while sICH was not associated ($p=0.26$). Regarding procedural complications: 5/298 (1.7%) were identified in the FPE group (four dissections and one emboli to a new territory. In contrast, 56/531 (10.5%) were identified in the non-FPE group (1 device fracture, 5 dissections, 20 emboli to a new territory, 25 perforations and 5 significant vasospasm).

Secondary analysis FPE versus non-FPE defined as mTICI 2c/3 in multiple passes

We performed further analysis on patients with FPE compared with patients in which a mTICI 2c/3 was achieved in multiple passes ($n=254$, 30.38%). Regarding predictors of FPE, occlusion site, unknown onset stroke, and baseline NIHSS were entered in a multivariable analysis. Baseline NIHSS remained a highly significant predictor of FPE

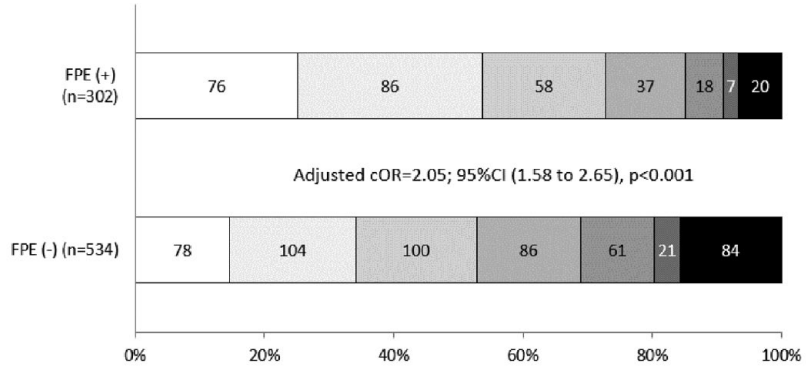

Figure 2. Distribution of Modified Rankin Scale at 90 days according to first pass effect.
cOR: common odds ratio; FPE: first pass effect. cOR calculated for one-point improvement in modified Rankin score using an ordinal logistic regression model.

Table 2. Comparison in efficacy and safety outcomes according to first pass effect.

Outcomes	FPE (−) (*n* = 534)	FPE (+) (*n* = 302)	OR (95% CI)[a]	*p*-Value[a]	OR (95% CI)[b]	*p*-Value[b]
Efficacy outcomes						
Δ NIHSS at 24 h, mean (95% CI)[c]	–2.80 (–3.41 to –2.20)	–5.64 (–6.45 to –4.83)	–2.84 (–3.86 to –1.82)[d]	<0.001	–2.88 (–3.90 to –1.86)[d]	<0.001
Favorable outcome	282/534 (52.8)	220/302 (72.8)	2.40 (1.77 to 3.25)	<0.001	2.20 (1.59 to 3.05)	<0.001
Excellent outcome	182/534 (34.1)	162/302 (53.6)	2.24 (1.68 to 2.99)	<0.001	2.03 (1.49 to 2.77)	<0.001
90-day mortality	84/534 (15.7)	20/302 (6.6)	0.38 (0.23 to 0.63)	<0.001	0.43 (0.25 to 0.72)	0.001
Safety outcomes						
Any intracranial hemorrhage	183/502 (36.5)	64/281 (22.8)	0.51 (0.37 to 0.72)	<0.001	0.55 (0.39 to 0.77)	<0.001
PH	30/506 (5.9)	3/284 (1.1)	0.17 (0.05 to 0.56)	0.004	NA	NA
SAH	53/506 (10.5)	17/284 (6.0)	0.54 (0.31 to 0.96)	0.035	NA	NA
sICH	6/505 (1.2)	1/284 (0.4)	0.29 (0.03 to 2.45)	0.26	NA	NA
Procedural complications	56/531 (10.5)	5/298 (1.7)	0.14 (0.06 to 0.37)	<0.001	NA	NA

CI: confidence interval; FPE: first pass effect; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; sICH: symptomatic intracranial hemorrhage.
Values expressed as no./total no. (%), unless otherwise stated.
[a]Calculated using FPE (–) group as reference.
[b]Calculated using FPE (–) group as reference after adjustment for independent predictors of FPE (hypertension and NiHSS).
[c]Mean change (95% CI) adjusted on baseline NIHSS score.
[d]Adjusted mean difference (FPE (+) vs FPE (–)).

(OR = 0.96, 95% CI 0.94–0.99, $p < 0.001$). Although an unknown time of stroke onset was also found to be an independent predictor of FPE (OR 1.45, 95% CI, 1.01–2.09, $p = 0.04$), we consider this finding devoid of clinical significance. (See Supplemental Table 1).

Regarding efficacy and safety outcomes of FPE versus mTICI 2c/3 in multiple passes, the reported odds ratios were similar to the preceding analysis (FPE vs mTICI 2b/3 in multiple passes – see Supplemental Table 2).

Discussion

In this large international cohort of patients with successfully recanalized primary MeVO, FPE was achieved in 36.1% of cases and was an independent predictor of excellent and favorable outcomes. Moreover, FPE was significantly associated with a more rapid reduction in NIHSS score at 24 h and a corresponding improvement in mRS shift at 3 months. FPE was associated with significantly lower overall rates of mortality and any ICH both in bivariate and adjusted models. Bivariate analysis showed a lower rate of procedural complications, periprocedural SAH, and lower rates of PH in the FPE group.

The rate of FPE in our cohort was marginally higher than FPE rates reported by a recent meta-analysis on LVO thrombectomy (36.1% vs 28%).[7] This might be expected and is in line with previous literature exploring the rate of FPE in smaller branches with lower thrombus burden.[8,16] For patients with LVO stroke treated with thrombectomy, three recent meta-analyses reported better outcomes in

patients for whom FPE was achieved than in patients recanalized in multiple passes.[4,7,17] According to these data, FPE is independently associated with a 55%–63% rate of favorable outcomes in LVO thrombectomy. This may be related to shorter duration of the procedure and lower rate of procedural complications.

Compared to previous meta-analyses on MeVOs, we have identified a slightly lower FPE rate. Still, these studies are difficult to compare as they have used various definitions for FPE, and MeVO sites are heterogeneously represented.[8,18] Our cohort achieved a favorable outcome in 72.8% of the FPE group and 52.8% of the non-FPE group. This is marginally higher than the overall functional independence of 51.3% reported in a recent systematic review of MeVOs.[8] However, our study included only patients with successful recanalization (mTICI $\geq$ 2b) at the end of the procedure for whom better functional outcomes are expected.[19] Given that the natural history of MeVOs is better than for LVOs and that a favorable functional outcome is expected in at least 68.3% of patients treated with tPA and 65.3% of those without any reperfusion treatment, nothing less than full reperfusion, ideally in one pass should be the goal when thrombectomy is offered to these patients, as minor complications (due to multiple passes) may prove to be more serious in the setting of MeVOs as compared to LVOs.[10]

Previous studies exploring the predictors of FPE in LVO stroke have yielded varying results. More distal occlusion (M1/M2 compared to ICA), older age, and varying technical factors such as combined approach or using balloon-guide catheters were consistently identified as predictors of FPE in LVOs.[1,4,20] It is difficult to explain why a history of hypertension would be an independent predictor of FPE, while in the same group, admission blood pressure does not seem to play a role. Perhaps patients with a history of hypertension had more frequent atherosclerosis-related strokes. Still, consistent stroke etiology data was unavailable for the overall cohort, preventing us from testing this hypothesis. Moreover, most of the literature data points toward an overall detrimental role of chronic hypertension in LVOs stroke.[21,22] Chronic hypertension seems to exert a deleterious effect on leptomeningeal collaterals, so the reverse would have been expected.[23] Thereby, a history of hypertension as a predictor of FPE might be just an accidental finding, and further data is necessary to clarify this finding.

Concerning stroke severity, this is in line with previous studies that showed that higher infarct volumes are associated with non-FPE recanalization.[6] The strength of this finding is supported by the consistent result obtained when comparing FPE with non-FPE in the subgroup of patients with mTICI 2c/3 recanalization (see Supplemental Analysis). This secondary analysis also reported unknown onset stroke as a predictor of FPE. Although of questionable value due to the low number of patients, this result might be driven by the selection of wake-up strokes with large perfusion mismatch and good collaterals. It would also be expected that in MeVOs, a lower NIHSS to be mediated by better collaterals which would favor a smaller thrombus burden and increased post-thrombus pressure, thereby facilitating passes.[24]

Theoretically, a complete secondary reperfusion with multiple passes in the same time window should lead to similar outcomes as first-pass reperfusion. However, FPE remained a significant factor for favorable outcomes in a previously matched cohort analysis.[25] Thus, the positive effect of FPE may be explained by the consistent association with adverse events in multi-pass recanalization. The higher rates of ICH, sICH, SAH, and procedural complications in the non-FPE groups reported by previous meta-analyses[4,7,17] might be mediated by a detrimental effect of multiple thrombectomy maneuvers, which may lead to subsequent vessel wall injuries and higher rates of bleeding that may ultimately modify the patient outcome.[26] While some may argue that stent-retriever choice and type would reduce hemorrhagic complications by controlling the pressure on distal vessel walls, a recent meta-analysis found no differences between stent types.[27] In our cohort, the non-FPE group showed significantly higher rates of procedural complications (10.5% vs 1.7%), SAH (10.5% vs 6%), PH (5.9% vs 1.1%), and any hemorrhage (36.5% vs 22.8%) as compared to the FPE group. This shared aggregation of complications and the high incidence of bleeding in the non-FPE group, even if it does not fit the criteria for sICH, may lead to worse outcomes and negate the benefit of reperfusion, by increasing brain inflammation and secondary injuries.[28–30] Moreover, longer procedure duration exposes the patients to potential contrast toxicity which may be linked to worse outcomes.

Randomized data about the efficacy and safety of EVT for MeVO is lacking, and several trials are ongoing (NCT05152524, NCT05029414, NCT05030142, NCT05151172). While these trials will shed light on the overall usefulness of EVT for these patients, this analysis suggests that when the vessel is not completely recanalized in one pass, complications increase, possibly diminishing the potential added benefit of EVT in this patient subgroup. Given the importance of FPE, we sought to identify predictors of FPE in our cohort. However, the only predictors of FPE were a history of hypertension and stroke severity. Previous work on LVO thrombectomy suggested that a combined approach and balloon guide catheters are independent predictors of FPE.[20,31] Our analysis did not identify any EVT technique impact on FPE. Still, this may be related to the retrospective study design and the heterogeneous nature of the techniques employed across different centers. A previously published sub-analysis showed no difference between stent-retriever and aspiration thrombectomy in MeVOs.[11] The blind mini-pinning technique was proposed as a potential solution to improve FPE rate and reduce

complications in MEVOs. The technique was recently improved using a quadriaxial approach to obliviate the need for a blind exchange and reduce the chance of unwanted complications due to inadequate vessel collapse or traction.[6,32,33] A balloon-guide catheter's added benefit might not be as evident in MeVOs as in LVOs. Most of these cases are performed with distal access catheters, even if they are not used for aspiration, and it was previously shown that this could reduce the utility of the balloon guide.[34] Moreover, in MeVOs reversal of flow may not be achieved due to the circle of Willis collaterals, and given the smaller diameter of the vessels, even small aspiration catheters may optimize distal flow control.[35]

Limitations

While this analysis was performed on the largest series reporting real-world data on FPE in MeVOs, there are several limitations inherent to the study's design. We have excluded patients with mTICI 2a or less and this might have led to a strong bias to evaluating predictors of FPE. Moreover, we chose to compare FPE defined as mTICI 2c/3 with recanalized patients mTICI 2b/3 as this approach facilitated the inclusion of more patients, excluding mTICI 2a or less patients also permitted to evaluate if the overall outcome results were driven by recanalization or by FPE. This approach provides important indications about real-life treatment scenarios, where the potential benefit of EVT in MeVOs may be restricted to subgroups obtaining an initial mTICI 2c/3 in one pass, as even in recanalized patients the number of complications related to multiple passes is far from negligible. Definitions of techniques employed by different sites, and different operator experiences, may have led to inconsistencies in the overall data. Our secondary analysis identified, unknown onset stroke as a predictor of first pass, the lack of data as to how those patients were selected for treatment and the low number of patients may are difficult to analyze. For example, a combined approach was not explicitly described as a blind mini-pinning technique. It might be that some of the cases were performed with a 6-Fr catheter in the M1 under continuous aspiration, which has been shown to collapse the M1 segment and possibly reduces the FPE.[36] So definite conclusions on technical outcomes can be hampered in this regard by inter-center variability. Moreover, images were not adjudicated by a core lab so the M2 category may be inconsistent (due to the different definitions employed by each center). Due to anonymization considerations, site information was not reported, and variations between sites could not be explored. Unfortunately, an adjusted model could not be performed for these secondary outcomes due to the low number of patients in each group (PH, sICH, SAH, procedural complications). Even though we pooled patients from several sites, our database was underpowered to identify significant differences between occlusion locations. Besides these inherent difficulties when pooling data from several sites, our results probably reflect the overall outcome expectations for MeVOs treated in a real-world setting between 2016 and 2021. Further, improvements in technique and potentially better technical outcomes could be contemplated with the advent of the MeVO randomized trials and dedicated distal access devices.

Conclusions

Complete or near complete first-pass recanalization was observed in little more than one-third of distal and medium vessel occlusion cases. It was independently associated with reduced stroke severity, an improved functional outcome at 90 days, lower 90-day mortality, and a lower rate of all-cause intracranial hemorrhage. It may be associated with reduced rates of periprocedural complications, symptomatic intracranial hemorrhage, and subarachnoid hemorrhage, but further studies are needed to validate these findings.

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Author contributions

Design of the study: RAR, VC, AD, AG; Data Collection: all authors; Data Analysis: RAR, MK, AD, AG; Drafting of the manuscript: RAR, VC, AD, AG; Project administration AD, AG; Supervision AD, AG; All authors read and agreed to the published version of the manuscript.

Declaration of conflicting interests

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Informed consent

This study was conducted in accordance with the Declaration of Helsinki and local regulations. The ethics committee of the coordinating center waived the patient consent form.

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Supplemental material

Supplemental material for this article is available online.

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