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Thrombectomy vs. medical management in low NIHSS acute anterior circulation stroke

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Abstract

Background – Endovascular thrombectomy (EVT) is highly effective for acute ischemic stroke with large vessel occlusion (LVO) and moderate to severe neurological deficits.

Objective: To undertake an effectiveness and safety analysis of EVT in patients with LVO and NIHSS≤6 using datasets of multicentre and multinational nature..

Methods – We pooled patients with anterior circulation occlusion from three prospective international cohorts. Patients were eligible if presentation occurred within 12 hours from last known well and baseline NIHSS≤6. Primary outcome was mRS 0–1 at 90 days. Secondary outcomes included neurological deterioration at 24 hours (change in NIHSS of ≥ 2 points), mRS 0-2 at 90-days and 90-day all-cause mortality. We used propensity score matching to adjust for non-randomized treatment allocation.

Results – Among 236 patients who fit inclusion criteria, 139 received EVT and 97 received medical management. Compared to medical management, the EVT group was younger (65 versus 72 years; p<0.001), had more proximal occlusions (p<0.001), and less frequently received concurrent intravenous thrombolysis (57.7% versus 71.2%; p=0.04). After propensity score matching, clinical outcomes between the two groups were not significantly different. EVT patients had an 8.6% (95% CI: -8.8–26.1%) higher rate of excellent 90-day outcome, despite a 22.3% (95% CI: 3.0–41.6%) higher risk of neurological deterioration at 24 hours.

Conclusions – EVT for LVO in patients with low NIHSS was associated with increased risk of neurological deterioration at 24 hours. However, both EVT and medical management resulted in similar proportions of excellent clinical outcomes at 90 days.

Introduction

Patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) usually suffer from severely disabling symptoms.[1] However, a significant number of LVO patients present with milder symptoms.[2] EVT is a standard of care for AIS due to LVO, but level 1A guideline recommendations for EVT are currently restricted to LVO patients with NIHSS≥6, since only a limited number of patients with low baseline NIHSS was enrolled in the randomized controlled trials.[3, 4]

AIS with NIHSS≤6 is routinely considered as "mild" and "non-disabling". However, one in four LVO patients with low baseline NIHSS suffer early neurologic deterioration resulting in poorer outcome.[5-7] From a patient perspective, milder deficits can restrict daily activities and can be devastating to their quality of life. Patients with LVO and low baseline NIHSS often have distinct clinical, demographic, and hospital arrival characteristics.[8] Multiple non-randomized studies have sought to evaluate the efficacy and safety of EVT in such patients and showed mixed results. These studies were mostly limited by their non-randomized design, small sample size, single-center experiences, varying practice or including patients treated prior to the efficacy of EVT was proven and incorporated into the (inter)national guidelines.[8-15]

The aim of our observational multicentre study was to assess the effectiveness and safety of EVT versus medical management in patients with LVO and NIHSS≤6 using recent data from comprehensive datasets and propensity score matching.

Methods

The data that support the findings of this study are available from the corresponding authors upon reasonable request. We retrospectively identified acute stroke patients with CT-angiography (CTA) proven anterior circulation occlusion and admission NIHSS≤6. For this purpose, we retrieved EVT data from the Safe Implementation of Treatments in Stroke – Thrombectomy registry (SITS-TBY) and compared them with medical management data derived from the INTERRSeCT and PROVE-IT study. The data sources are described in further detail below and inclusion and exclusion criteria for each study are presented in Table 1.

Standard Protocol Approvals, Registrations, and Patient Consents:

Permissions to analyze data for the SITS-TBY (a non-profit, quality improvement-driven, international) registry were provided by the ethics committee of St. Anne's University Hospital, Brno, Czech Republic; individual patient consent for the SITS-TBY registry was not sought. The PROVE-IT study used a waiver of consent which was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written informed consent was provided by the patient or a surrogate for the INTERSeCT study. The reviews of the Institutional Review Boards (IRB) for each study determined that informed consent was not required for this current pooled analysis. The study protocol was approved by scientific committees of each study.

Endovascular data source:

National EVT data from the Czech Republic were extracted from the population-based SITS-TBY registry from January 2015 to December 2018 to cover the time period after the publication of positive endovascular trials.[16-20] The SITS-TBY registry represents a non-profit, research-driven, international registry collecting data on endovascular treatment. Anonymized patient-level data are entered at each stroke center either by a research nurse or physician at discharge or at 90-days follow-up. There has been no formal audit of the Czech SITS-TBY or SITS-TBY data. However, 12 (out of 15) comprehensive stroke centers participated in the registry in 2016 as part of a quality improvement program. Random hospital-level metrics reported to the Czech Ministry of Health were cross-checked with the SITS data and showed high level of consistency (unpublished).[21] Additionally, a nationwide

questionnaire survey run in 2016 did not show major differences in clinical practise including neuroimaging, logistics and treatment standards in all 15 comprehensive stroke centers in the Czech Republic.[22] Furthermore, since 2016, the Czech Stroke Society has been providing feedback quarterly to all participating stroke centers on number of EVT cases and time metrics based on the data from the registry. Patients for endovascular treatment in the Czech Republic are selected through CT and (multiphase) CTA imaging.

Medical management data source:
Medical management was based on current guidelines (Canadian Stroke Best Practise Recommendations), American Heart and Stroke Association), including intravenous alteplase in patients presenting within the first 4.5 hours from last seen normal. In patients not eligible for intravenous alteplase, an antiplatelet agent was administered on day 1, unless there was an indication for early anticoagulation.

The two non-thrombectomy cohorts were selected from the multicentre international observational studies: 1) Measuring Collaterals with Multi-phase CT Angiography in patients with Ischemic Stroke (PROVE-IT, patient enrolment between July 2014 to October 2017); and 2) Identifying New Approaches to Optimise Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography study (INTERRSeCT, patient enrolment between March 2010 to March 2016).

PROVE-IT was a prospective multi-center cohort study of 500 consecutive patients with AIS presenting within 12 hours of stroke symptom onset with evidence of intracranial occlusion on routine CTA. The primary aim of this trial was to evaluate imaging selection for thrombolysis and intra-arterial (endovascular) decision-making in the setting of AIS.[23] INTERRSeCT was a multicentre prospective cohort study that enrolled 575 patients with acute ischemic stroke with intracranial thrombi documented via CTA. The study included patients with a wide range of clinical presentations (within 12 hours from last known well), occlusion sites, and thrombus characteristics to identify clinical and imaging variables associated with recanalization with or without intravenous thrombolysis.[24]

For the current study, we only included patients who were independently functioning in the community immediately prior to their stroke (estimated baseline modified Rankin scale 0-2).

Patients were further eligible if they presented to the emergency department with symptoms consistent with acute ischemic stroke 12 hours from time last known well, baseline NIHSS≤6, and baseline CTA with the evidence of symptomatic intracranial occlusion (internal carotid artery [ICA] and/or middle cerebral artery [MCA] including M1 and proximal M2 segments). Patients with the primary posterior circulation occlusions were excluded.

Demographics, Variables, and Measurements

Information on baseline demographics, vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, smoking history (current/past), congestive heart failure), time last seen normal, NIHSS score (range, 0-42, with higher scores indicating severe stroke), occlusion location (ICA, M1, M2 MCA), prior use of anticoagulation, prior use of antithrombotic treatment, intravenous alteplase administration (if applicable although many low NIHSS patients are not thrombolysed), were collected. Other clinical endpoints were 24-h NIHSS and functional outcome at 90 days measured on the mRS.

Study outcomes

Modified Rankin Scale 0–1 at 90 days was chosen as the primary outcome because patients with mild deficits at baseline are more likely to have excellent outcomes. Secondary outcomes were the neurological deterioration at 24 hours (defined as increase of NIHSS score by 2 or more points)[25], mRS 0-2 at 90 days and all-cause mortality at 90 days.

Missing/incomplete data:

Among 236 patients, four had missing baseline NIHSS, five missing prior anticoagulation history, six missing prior smoking history, six prior atrial fibrillation history, one missing prior hypertension and prior dyslipidemia history; 14 missing 24-h NIHSS, 13 missing 90-days mRS. We imputed the missing NIHSS baseline values with the group median from the remaining available data and imputed “no” for missing binary variables. The 13 missing values for 90-day mRS were again imputed with the median of the remaining available data. Since all missing mRS occurred in the EVT group, we performed additional sensitivity analysis assuming that the missing 90-day mRS values indicated that the person did not reach a favorable outcome and was disabled/dead (i.e. worst-case scenario), did achieve a favorable outcome (i.e. best-case scenario), and omitted cases with missing mRS

scores. For the 14 missing values of 24h-NIHSS (all but one one from the EVT group) we assumed that the patients had neurological deterioration (i.e. worst-case scenario).

Data about intracranial hemorrhages were missing and unverifiable in the SITS-TBY registry and could thus not be analyzed in our current study. Since the SITS-TBY registry is a study of implementation of thrombectomy in routine clinical practice, it was not mandated that time metrics were being collected. Onset-to-treatment times were thus not available for our analysis.

Statistical analysis

Standard descriptive statistics were used to measure central tendency and variability of baseline characteristics. Ordinal/continuous variables were compared by the Mann-Whitney test or t-test based on their distribution. Categorical variables were compared using the Fisher's exact test.

Since our data were not randomized, we used propensity score matching to estimate the adjusted treatment effect of EVT compared to the best medical management, accounting for differences in baseline variables. We used the treatment effect option with propensity score matching in STATA version 14.2 (College Station, TX). Derivation of standard error accounted for the fact that propensity scores are estimated rather than known. Propensity scores were derived from a multivariable logistic regression model that calculates the treatment probability for each subject. This model was adjusted for the following clinically relevant baseline variables: sex, age, occlusion location, thrombolysis status, baseline mRS, prior antithrombotic treatment and NIHSS. The propensity scores were then used to impute the missing potential outcome (if a subject received EVT then medical management is considered counterfactual and if the subject received medical management then EVT is considered counterfactual) for each subject by taking the outcome of a similar subject that received the other treatment level (or multiple subjects if there was a tie for similarity). Similarity between subjects was based on the propensity scores. Common support was assessed using an overlap plot and examination of mean propensity scores by treatment group and quintiles and found to be adequate (Figure 1 and Table 2). The treatment effect was computed by taking the average of the difference amongst each EVT and medical management pairs, where outcomes were either observed or derived as the counterfactual from the propensity matching process and presented as a risk difference with 95% confidence

interval (CI). We used this method of matching and analysis for our primary, secondary and safety outcomes. We visualized the unadjusted data and the results of our primary analysis using horizontally stacked bar graphs. Sensitivity analysis was performed for the primary outcome using the worst-case scenario, best-case scenario and by omitting cases with missing primary outcome as described above.

All tests were two-sided and the significance level was considered as 0.05. Statistical analyses were performed using STATA version 14.2 (College Station, TX).

Data Availability

Anonymized data will be shared by reasonable request from a qualified investigator.

Results

Baseline Characteristics

Our pooled dataset resulted in 281 patients with LVO and mild symptoms. We excluded eleven patients who were not independent at baseline, 33 patients with distal M2, M3 and no occlusion, and one patient treated with tenecteplase (TNK). This left 236 patients for analysis; 139 received EVT and 97 medical management. The two groups had similar baseline NIHSS, baseline mRS and baseline vascular risk factors. The EVT group was younger (65 versus 72 years), with more proximal occlusions (50.4% M1 and 15.8% ICA versus 25.8% M1 and 2.1 ICA), and less concurrent intravenous alteplase treatment (57.7% versus 71.2%) as illustrated in Table 3.

Primary and secondary outcomes

Ninety-day excellent outcome (mRS 0-1) was achieved in 62.7% (n=148) of patients overall, with no difference between the EVT and medical management group (61.9 % vs 63.9 %, p=0.785) in unadjusted analysis. The raw distribution of mRS scores between the EVT and medical management group at 90 days is shown in Figure 2. After propensity score matching, patients in the EVT group had an 8.6% (95% CI: -8.8% – 26.1%) higher chance of excellent outcome at 90 days compared to the medical management group. The distribution of mRS scores of the EVT and medical management group at 90 days after the propensity score matching is presented in Figure 3. The result was unchanged in sensitivity analysis using the worst case scenario (missing outcomes assumed to have achieved mRS 2-6) and when cases with missing mRS were omitted (p=0.33 and p=0.250, respectively). However, assuming best-case scenario (missing outcomes actually achieved mRS 0-1), patients in the EVT group had a 17.6% (95% CI: 0.01% – 35.4%) higher chance of excellent outcome at 90 days compared to the medical management group.

Unadjusted analyses of the secondary outcomes are shown in Table 4. After propensity score matching, patients in the EVT group had a 22.3% (95% CI: 3.0% – 41.6%) higher risk of neurological deterioration at 24 hours compared to patients in the medical management group. Patients in the EVT group also had a 2.2% (95% CI: -3.6% - 7.9%) higher risk of death from any cause within the first 90 days after the index event compared to the medical management group.

Discussion

In our study endovascular treatment and best medical management for large vessel anterior circulation occlusion in patients presenting with low NIHSS resulted in similar proportions of excellent functional outcome at 90 days and comparable all-cause 90-day mortality. This outcome parity occurred despite an increased endovascular treatment risk of neurological deterioration at 24 hours.

In keeping with our results, other smaller multicenter studies have utilized propensity score matching and found no significant difference in the excellent functional outcome at 90-days.[9-11] Although the study by Nagel *et al* (77 matched pairs) showed a 14.4% absolute difference in good clinical outcome (84.4% versus 70.1%, p=0.03) defined as mRS 0-2 and an adjusted OR of 3.1 (95% CI, 1.4-6.9) favoring immediate EVT, there was no such difference seen for excellent outcome defined as mRS 0-1 at 90 days.[10] Additionally, the study enrolled 7% of patients with basilar occlusions and 6% of patients with initial mRS>2 (20/300 patients). In the study by Haussen *et al*, the protocol also allowed inclusion of patients with basilar occlusions, which then made up 23% of the EVT group.[12] These and other previously published (mostly single-center) studies have selected individual sites with variability in their approach to patient care and differing local treatment guidelines. A more recent study by Asdaghi *et al* looked at over 400 registry patients and found an association of EVT with favorable discharge outcomes and ambulatory status.[8] However, the 90-day outcomes as well as the occlusion status and thrombus location were not documented consistently. All three of these studies included patients who received endovascular treatment before the publication of positive randomized control trials in 2015 and thus the incorporation of endovascular treatment as a standard of care into national guidelines. Thus, the results of these studies might be reflective of the heterogeneity in workflow and experience with such patients and might not be representative of the current clinical practice.

We found no difference in all-cause 90-day mortality in our study, which is in congruence with the smaller multicentre studies of Nagel *et al* and Dargazanli *et al.* In the study of Sarraj *et al*, the patients undergoing EVT had higher mortality (8.9% versus 1.1%, p=0.03) possibly driven by increased risk of symptomatic ICH (5.8% versus 0%).[9-11] Similarly, Asdaghi *et al* reported mortality of 5.2% and symptomatic ICH rates of 4.5%.[8]

Endovascular treatment was associated with increased risk of neurological deterioration at 24 hours (defined as ≥ 2 points increase of the NIHSS scale) in our propensity-score matched analysis. One possible explanation might be the occurrence of symptomatic ICH with the endovascular treatment. Neurological deterioration might have also been more apparent on formal testing in a setting of mild initial symptoms and thus been more diligently scored. Further, other complications of EVT including embolic events into other arterial territories, arterial access adverse events such as haemorrhage, retroperitoneal hematoma and pseudoaneurysm formation may impact 24-hour assessment.

Multiple studies have shown that since low NIHSS patients are generally considered too mild for thrombolysis and endovascular treatment, up to one third end up disabled or dead at the 90-day follow-up when left hyperacutely untreated.[26-29] It is known that in stroke due to (large) vessel occlusion, there is a clear relationship between recanalization and favorable/excellent outcome even though our current study and various other have shown differing effect sizes (from 8.6% to 14.4%)[10, 30] Yet, interventional treatment, whether medical with intravenous thrombolysis or surgical with endovascular thrombectomy has possible harm. The value of a future randomized controlled trial in this patient cohort is thus not to show the benefit of EVT but rather to assess if the benefit outweighs the potential harm of the treatment. Data about intracranial hemorrhages were missing and unverifiable in the SITS-TBY registry and could thus not be analyzed in our current study. But two previous studies in low NIHSS strokes that have specifically measured sICH found a notable difference between the EVT and medical management group (Sarraj *et al* 5.8% vs. 0% [p=0.02], Nagel *et al* 5% vs. 1.4% [p=0.08]).[9, 10] However, these are sICH risks that we accept for moderate-severely disabling stroke and the acceptable risk of sICH must be significantly less in low NIHSS strokes to justify the risk of death and disability as a complication of EVT. Due to this uncertainty in numbers, despite several analyses from groups around the world, a well-designed randomized controlled trial would be able to finally answer the question about the risk-benefit-ratio of EVT for low NIHSS strokes.

The strength of our study is its multicenter and multinational nature of the utilized datasets. The national population-based EVT data were extracted from the SITS-TBY registry from January 2015 to December 2018 in order to cover the time period after the publication of positive endovascular trials and as such reflect current clinical practice. Our study is

limited by its retrospective nature and even though we tried to account for confounding by using advanced statistical methods, there is still a risk of residual confounding due to unmeasured variables. For example, even though we incorporated occlusion location into our propensity score model, we were unable to also incorporate a measure of early ischemic change since these data were not available. Furthermore onset-to-treatment times were not available for our analysis. Although twelve of total 15 comprehensive stroke centers in the Czech Republic contributed to the SITS-TBY registry during the study period, our previous study showed that over 80% of all thrombectomy cases in the Czech Republic were reported to the registry in 2016.[31] We also had no data on the use of anesthesia/sedation during EVT available. Blood pressure changes during induction of general aneasthesia may risk penumbral tissue perfusion and might thus contribute to the neurological deterioration at 24 hours.[32, 33]The mRS, even though one of the most commonly used outcome markers in stroke and captured by the three observational data sources we have used, lacks sensitivity at the minor disability end of the scale and we might thus have not been able to detect a significant difference in our primary outcome. Our matched analysis is larger than the sample size of prior studies but still might have affected our statistical power to detect a true difference. Race and ethnicity were not collected in the three datasets utilized.

In conclusion, our multicenter observational post-hoc study showed that EVT for LVO in patients with low NIHSS resulted in similar 90-day outcomes compared to the best medical management despite an increased risk of neurological deterioration at 24 hours.

Table 1. – Inclusion and exclusion criteria of utilized study cohorts.

	SITS-TBY	INTERRSeCT	PROVE-IT
Inclusion Criteria	- Presentation to the emergency department with symptoms consistent with ischemic stroke 6 hours (2015 – 2017) or 24 hours (2018) from last known well - Age at least 18 years - Baseline CTA with evidence of large vessel occlusion amenable for endovascular treatment	- Presentation to the emergency department with symptoms consistent with ischemic stroke 12 hours from last known well - Age at least 40 years - Baseline CTA (before alteplase bolus, if given) with evidence of a symptomatic intracranial thrombus (ie, internal carotid artery [ICA], middle cerebral artery [MCA] proximal segment [proximal M1], MCA distal segment [distal M1], MCA M2 segment [M2], MCA M3 segment [M3], anterior cerebral artery, or posterior cerebral artery)	- Patient presenting to the emergency department with symptoms consistent with ischemic stroke - Age > 18 yrs - Baseline imaging including multi-phase CTA done within 12 hours of stroke symptom onset and initiated before recanalization therapy - Evidence of a visible and symptomatic intracranial occlusion on baseline CT-angiography (intracranial ICA, M1 MCA segment +/- intracranial ICA, proximal M2 MCA) - Treatment with

			IV tPA and/or IA therapy
Exclusion Criteria	- Contraindications against having EVT performed	- primary vertebrobasilar artery occlusions - renal impairment (estimated creatinine clearance <60 mL/min) - contrast allergy - hypoglycemia (serum glucose <36 mg/dL) - unlikely to participate in follow-up	- Intracranial hemorrhage (ICH) identified on baseline CT - Previous moderate to large stroke in the ipsilesional hemisphere - Modified Rankin Scale > 2 at baseline - Unable to have CT-angio performed due to recent estimated creatinine clearance eCCr<60 ml/min, contrast allergy or other reasons - Participation in another study that results in the patient receiving an investigational drug or therapy - Any terminal illness (patient not expected to survive > 1 year)

Table 2. – Mean Propensity Scores by Quintiles and Treatment Group

	Propensity Score Quintile	N° of observations	Mean Propensity Score
Medical management	1	16	0.1493147
	2	32	0.3243983
	3	32	0.5053389
	4	11	0.7024942
	5	6	0.9026154
Thrombectomy	1	-	-
	2	15	0.3160577
	3	34	0.5075231
	4	37	0.71144248
	5	53	0.9148278

Table 3. Baseline Characteristics before Propensity Score Matching Process

Variable	Medical Management group N = 97	Endovascular group N =139
Median age in years (25% – 75%)	72 (63 – 80)	65 (55 – 75)
Sex, male, %	48.9	43.4
Occlusion site, %		
• Internal carotid artery	2.1	15.8
• Tandem occlusion	2.1	3.6
• M1 segment	25.8	50.4
• Proximal M2 segment	70	30.2
Median baseline NIHSS (25% – 75%)	5 (4 – 6)	4 (3 – 6)
Baseline modified Rankin Scale, %		
• 0	87.6	87.8
• 1	7.2	5.0
• 2	5.2	7.2
Intravenous alteplase treatment, %	71.2	57.7
Prior anticoagulation, %	9.4	10.3
Prior antithrombotic treatment, %	25.2	44.3
Hypertension, %	65.5	68
Diabetes mellitus, %	14.4	10.8

Dyslipidemia, %	26.6	38
Atrial fibrillation, %	23.7	28.9
Smoking current/past, %	28.9	22.3
Congestive heart failure, %	6.5	3.1

Legend: NIHSS means National Institutes of Health Stroke Scale

Table 4. Unadjusted Outcome Analysis

Outcome	Medical Management group N = 97	Endovascular group N =139	Fisher's exact test, p-value
Modified Rankin Scale score 0-1 at 90 days, %	63.9 %	61.9	0.785
Neurological deterioration at 24 hours, %	10.3	30.2	<0.001
Modified Rankin Scale score 0-2 at 90 days, %	79.4	69.1	0.100
All-cause mortality at 90 days, %	3.1	5.0	0.532

Figure Legend

Figure 1: Overlap Plot of Propensity Scores to Check for Common Support

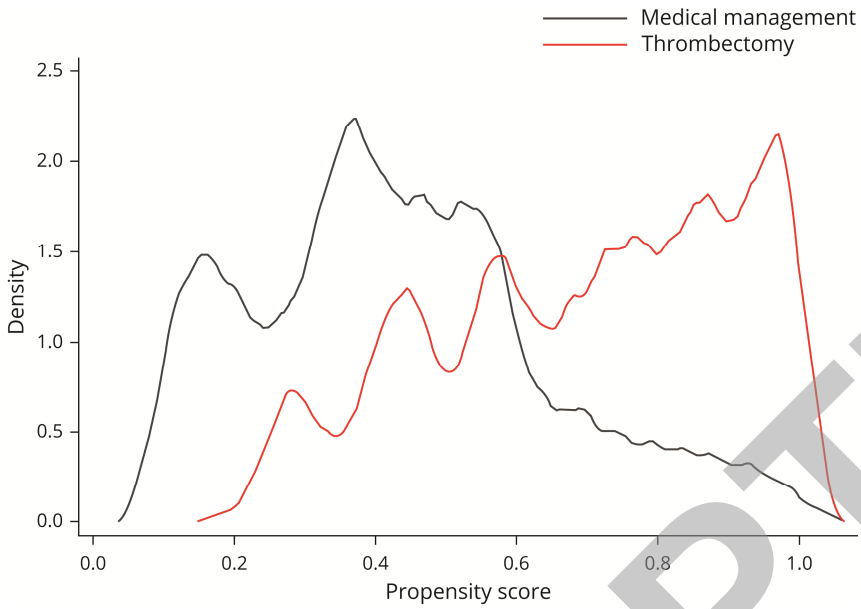


Figure 2: Unadjusted analysis of 90-day modified Rankin Scale shift

Legend: EVT means endovascular treatment, MM medical management, mRS modified Rankin Scale.

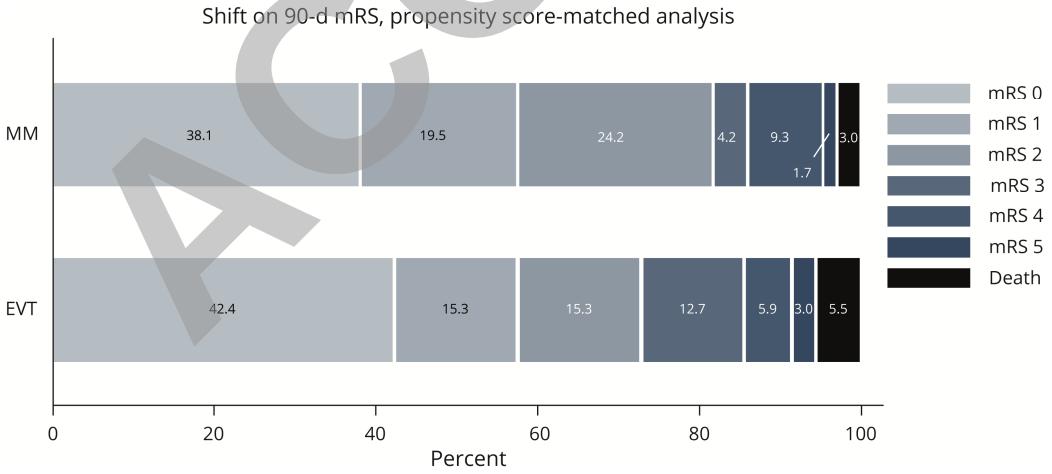
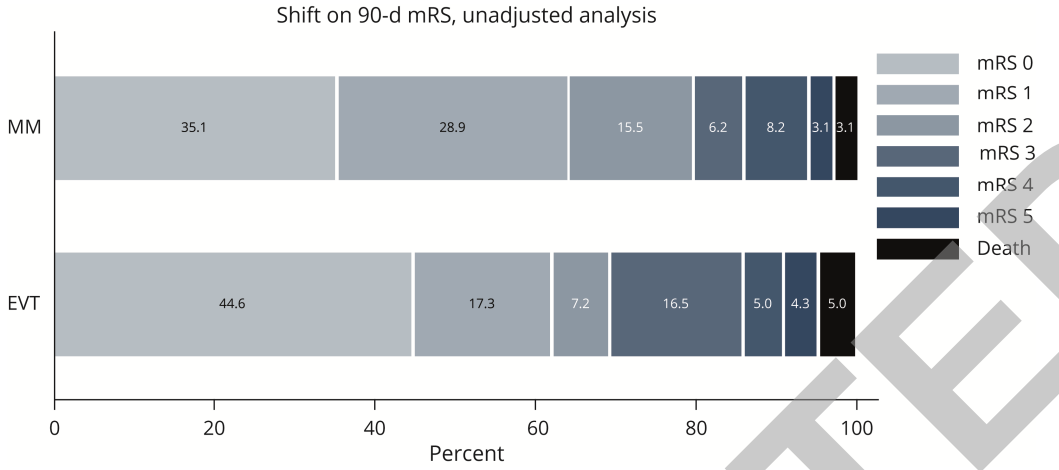


Figure 3: Propensity-Score matched analysis of 90-day modified Rankin Scale shift

Legend: EVT means endovascular treatment, MM medical management, mRS modified Rankin Scale.



Appendix 1: Authors

Name	Location	Contribution
Ondrej Volny MD, PhD	Masaryk University, Brno, Czech Republic	Designed and conceptualized the study; interpreted the data; drafted the manuscript for intellectual content
Charlotte Zerna MD, MSc	University of Calgary, Calgary,Canada	Designed and conceptualized the study; analyzed the data; created the tables and figures; interpreted the data; drafted the manuscript for intellectual content
Ales Tomek MD, PhD	Charles University, Prague, Czech Republic	Data acquisition; revised manuscript for intellectual content
Michal Bar MD, PhD	University Ostrava, Czech Republic	Data acquisition; revised manuscript for intellectual content
Miloslav Rocek MD, PhD	Charles University, Prague, Czech Republic	Data acquisition; revised manuscript for intellectual content
Radek Padr MD	Charles University, Prague, Czech Republic	Data acquisition; revised manuscript for intellectual content
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