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ARTICLE CLASS OF EVIDENCE

Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms

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Abstract

Objective
To compare outcomes after endovascular therapy (EVT) and IV thrombolysis (IVT) in patients with stroke with emergent large vessel occlusion (LVO) and mild neurologic deficits.

Methods
This was a retrospective analysis of patients from the Swiss Stroke Registry with admission NIH Stroke Scale score ≤5 and LVO treated by EVT (± IVT) vs IVT alone. The primary endpoint was favorable functional outcome (modified Rankin Scale [mRS] score 0–1) at 3 months. Secondary outcomes were independence (mRS score 0–2), mRS score (ordinal shift analysis), and survival with high disability (mRS score 4–5). Safety endpoints were mortality and symptomatic hemorrhage.

Results
Of 11,356 patients, 312 met the criteria and propensity score method matched 108 in each group. A comparably large proportion of patients with EVT and IVT had favorable outcome (63% vs 65.7% respectively; odds ratio 0.94, 95% confidence interval 0.51–1.72; $p = 0.840$). Patients with EVT showed a nonsignificant trend toward higher mRS score at 3 months ($p = 0.717$), while the proportion of surviving patients with high disability was comparably very low in both groups ($p = 0.419$). Mortality was slightly higher among those with EVT (9.3% vs 2.8%; $p = 0.06$), and symptomatic intracranial hemorrhage was a rare event in both groups (2.8% vs 0%; $p = 0.997$).

Conclusions
In acute ischemic stroke, EVT and IVT appear similarly effective in achieving favorable outcome at 3 months for patients with LVO and mild neurologic symptoms. EVT might be marginally inferior to IVT regarding outcome across all levels of disability and mortality. Further studies are required to determine whether certain subgroups of patients with LVO and mild symptoms benefit from EVT.

Classification of evidence
This study provides Class III evidence that patients with LVO and mild symptoms receiving either EVT or IVT had similar favorable functional outcomes at 3 months.

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Glossary

AIS = acute ischemic stroke; **CA** = carotid artery; **CI** = confidence interval; **EVT** = endovascular therapy; **HERMES** = Heart Failure Molecular Epidemiology for Therapeutic Targets; **IVT** = IV thrombolysis; **LVO** = large vessel occlusion; **mRS** = modified Rankin Scale; **mTICI** = modified Thrombolysis in Cerebral Infarction; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PRISMS** = Potential of rtPA for Ischemic Stroke With Mild Symptoms; **PS** = propensity score; **sICH** = symptomatic intracranial hemorrhage.

Endovascular therapy (EVT) is the most effective method to obtain recanalization and functional independence in patients with acute ischemic stroke (AIS) with an emergent large vessel occlusion (LVO) of the anterior circulation and moderate to severe stroke symptoms (NIH Stroke Scale [NIHSS] score ≥6).[1]

Whether patients with LVO and mild stroke symptoms (NIHSS score ≤5) also benefit from EVT remains unknown. However, patients with acute stroke with mild deficits (NIHSS score ≤5) not promptly treated by recanalization therapies are more susceptible to unfavorable outcome, with LVO being the main predictor of clinical deterioration[2–7] On the other hand, IV thrombolysis (IVT) is generally considered efficacious and safe in patients with mild deficits.[8–10] A single randomized controlled trial comparing IVT and aspirin in this population provided inconclusive results, and patients were not stratified according to LVO presence.[11] Data on efficacy and safety of EVT in patients with mild symptoms (NIHSS score ≤5) and LVO are contradictory and come mainly from small, nonrandomized observational studies.[12–15] Recently, the benefit of EVT in these patients has been doubted,[16] but a direct comparison of EVT and IVT alone has not been performed. Consequently, there are no specific guidelines for the management of patients with LVO presenting with mild symptoms (NIHSS score ≤5).[17]

We conducted this multicenter study to evaluate the comparative efficacy and safety of EVT (with or without IVT) vs IVT alone in patients with acute stroke, LVO, and NIHSS score ≤5 using a propensity score (PS)–matching approach.

Methods

Study cohort

We performed a multicenter retrospective analysis of prospectively collected data in the Swiss Stroke Registry. The Swiss Stroke Registry is an institutional review board–approved national web-based registry that was started in January 2014 and designed to collect a standardized dataset of all patients with ischemic stroke hospitalized in certified stroke units and comprehensive stroke centers across Switzerland. The database is managed by the Clinical Trial Unit of the University of Basel and follows the recommendations of the European Stroke Organisation.[18] Clinical, radiologic, and detailed information on therapies performed on patients with acute stroke in the emergency room is carefully collected. This information includes prestroke functional status, as measured by the modified Rankin Scale (mRS), prestroke medical treatments (e.g., anticoagulants), NIHSS score at admission, imaging results (brain angio-CT or angio-MRI), presence of LVO, occlusion site, and performed treatments (i.e., IVT and/or EVT). Clinical data and neurologic and functional outcomes during hospitalization and at 3 months after stroke are also collected. Clinical evaluations, as well as NIHSS and mRS assessments, are performed by certified stroke neurologists as part of their clinical activity. If an in-person visit is not possible at 3 months, mRS score is assessed by a phone interview with mRS-certified examiners.

Inclusion and exclusion criteria

Patients fulfilling the following criteria were included in the study: (1) age ≥18 years with clinical and radiologic diagnosis of AIS, (2) presence of an LVO (carotid artery [CA], middle cerebral artery [M1, M2] on acute cerebral angiographic-imaging (angio -CT or angio- MR), (3) presenting with mild neurologic deficits (NIHSS score ≤5) on admission and before treatment, and (4) treated with EVT (± IVT) or IVT (recombinant tissue plasminogen activator) alone. All patients included in the analysis were first-line treated in comprehensive stroke centers, where endovascular treatment is routinely performed.

We excluded patients with the following conditions from the analysis: patients without prestroke functional independence (i.e., mRS score >2) and patients with occlusions of the vertebral artery, basilar artery, posterior cerebral artery, or middle cerebral artery segments that are more distal.

Outcomes

The primary research question of this observational study for Class III evidence was whether EVT (EVT with or without IVT) had favorable functional outcome at 3 months similar to IVT alone, defined as an mRS score of 0 to 1 at 3 months after stroke.

Secondary functional outcomes at 3 months were the proportion of functionally independent patients (i.e., mRS score of 0–2), global mRS assessment evaluated by mRS score shift analysis, and proportion of patients surviving with high disability (i.e., mRS score 4–5). Safety endpoints were mortality at 3 months and occurrence of symptomatic intracranial hemorrhage (sICH) defined as ≥4-point worsening of the NIHSS score associated with brain hemorrhage.

Exploratory outcomes included potential differences in favorable outcome and mortality between patients undergoing EVT alone vs IVT + EVT vs IVT alone, differences in

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favorable outcome and mortality within the subgroups of PS-matched individuals with CA/M1 or M2 occlusions, and the potential influence of reperfusion grade as measured by the modified Thrombolysis in Cerebral Infarction (mTICI) scale on favorable outcome and mortality in patients with EVT.

Statistical analyses

We described categorical variables by counts and percentages and continuous and ordinal variables by median and interquartile ranges. After the selection of patients based on inclusion criteria, patients with IVT and EVT were matched 1:1 with PSs to limit the potential bias due to imbalance in baseline covariate distributions. PSs were based on the main variables that could potentially influence treatment choice (EVT vs IVT) and included age, sex, baseline NIHSS score, prestroke mRS score, time between stroke and treatment initiation, vessel occlusion site (CA, M1, M2), and prestroke anticoagulation therapy (presence vs absence). We used a conservative caliper size of 0.1 SDs of the logit of the PS to provide adequate matching.

We compared binary outcomes (e.g., favorable functional outcome at 3 months) between IVT and EVT using multivariate logistic regression models and performed shift analysis on mRS score at 3 months after stroke using a multivariate ordinal regression model. All regression models included type of treatment (EVT ± IVT vs IVT alone) as the main independent variable, as well as the same variables used to build the PSs to adjust for remaining imbalances between the 2 groups.

Subgroup analyses were performed by further stratifying patients with EVT on the basis of whether IVT was also performed (i.e., EVT alone vs EVT + IVT vs IVT alone). We similarly tested the association between treatment status and both primary outcome and mortality in PS-matched patients with either CA/M1 or M2 occlusions separately. We also tested the association between the reperfusion grade as measured by the mTICI scale on favorable outcome and mortality in patients with EVT.

We performed all analyses using R (r-project.org/) and the R packages MASS and nonrandom.

Standard protocol approval, registration, and patient consent

The study complied with the Declaration of Helsinki. We obtained ethics approval from institutional review boards of all participating centers. In accordance with national law, patients were informed about the use of their routinely collected data for research purposes. Patients who denied use of their data were excluded from the analysis.

Data availability

Anonymized data will be shared on request from any qualified investigator.

Results

Patient selection and baseline characteristics

Of 11,356 patients with acute stroke admitted to our stroke centers between January 1, 2014, and July 31, 2017, 312 met the inclusion criteria. Of these, 137 were treated with EVT (n = 68 with EVT alone, n = 69 with EVT + IVT) and 175 with IVT only. Baseline characteristics are shown in table 1, with the most prominent differences between EVT and IVT being the occlusion site (EVT: CA 19.7%, M1 38%, M2 42.3%; IVT: CA 12.6%, M1 12%, M2 75.4%; $p < 0.001$) and onset-to-treatment time (EVT 3.33 [1.83–6.7] hours, IVT 2.07 [1.45–2.76] hours; $p < 0.001$). There were no differences between the 2 groups in terms of age, sex, prestroke mRS score, preanticoagulation treatment, and NIHSS score at admission (table 1).

After matching with the PS method, 108 patients in each group were available for analysis. Baseline characteristics and outcome variables of PS-matched patients are listed in table 2. As expected, baseline differences between the 2 groups were greatly reduced with the now-comparable occlusion sites ($p = 0.601$). However, despite PS matching, a statistically significant difference remained in terms of onset-to-treatment time (EVT 3.32 [2.08–6.4] hours, IVT 1.95 [1.43–2.52] hours; $p < 0.001$). Among patients with EVT, 84% of them reached substantial reperfusion (mTICI score 2b–3).

Primary outcome

The proportion of patients with a favorable outcome at 3 months (mRS score 0–1) was 63% in patients with EVT and 65.7% in patients with IVT. This difference was not statistically significant in the multivariate regression model adjusted for age, sex, baseline NIHSS score, prestroke mRS score, time from stroke to treatment initiation, vessel occlusion, and prestroke anticoagulation therapy (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.51–1.72; $p = 0.840$; table 3). Prestroke mRS score was negatively associated with a favorable outcome at 3 months (table 3). The 90-day mRS outcomes stratified by treatment status are shown in the figure.

Secondary outcomes

The proportion of patients who were independent at 3 months (mRS score 0–2) was 79.7% in patients with EVT and 86.1% in patients with IVT. In the multivariate analysis, the odds of reaching independence at 3 months was similar in both groups (adjusted OR 0.62, 95% CI 0.28–1.37; $p = 0.240$; table 3). Older age was negatively associated with the chance of reaching independence at 3 months (table 3). The 3-month mRS score shift analysis showed overall a nonsignificant trend toward greater mRS score in patients with EVT than in those with IVT (figure), with no significant difference between the 2 groups in the ordinal regression model (adjusted OR 1.09, 95% CI 0.67–1.78; $p = 0.717$; table 4). Survival with high disability (mRS score 4–5) was rare in both groups (5.5% vs 3.7%; adjusted OR 1.77, 95% CI 0.44–7.01; $p = 0.419$). A higher prestroke mRS score was associated with both a higher mRS score at 3 months and survival with high disability (table 4).

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Table 1 Baseline characteristics and outcome variables of unmatched EVT- and IVT-treated patients

Variable	EVT (n = 137)	IVT (n = 175)	*p* Value
Age, y	69.7 (56–79)	71.3 (62.1–79.1)	0.205
Sex, n (%)			
F	72 (52.6)	79 (45.1)	0.236
M	65 (47.4)	96 (54.9)	
Prestroke mRS score			
0	105 (76.6)	146 (83.4)	0.173
1	26 (19)	20 (11.4)	
2	6 (4.4)	9 (5.2)	
Anticoagulant treatment, n (%)			
No	120 (87.6)	161 (92)	0.271
Yes	17 (12.4)	14 (8)	
NIHSS score (admission)	4 (2–5)	3 (2–5)	0.533
Occlusion site, n (%)			
CA	27 (19.7)	22 (12.6)	<0.001
MCA (M1)	52 (38)	21 (12)	
MCA (M2)	58 (42.3)	132 (75.4)	
Onset-to-treatment time, h	3.33 (1.83–6.7)	2.07 (1.45–2.76)	<0.001
sICH, n (%)			
No	129 (94.9)	172 (98.3)	0.168
Yes	7 (5.1)	3 (1.7)	
mRS score at 3 mo, n (%)			
0	39 (28.5)	56 (32)	0.150
1	43 (31.4)	65 (37.1)	
2	24 (17.5)	33 (18.9)	
3	10 (7.3)	10 (5.7)	
4	6 (4.4)	4 (2.3)	
5	1 (0.7)	2 (1.1)	
6	14 (10.2)	5 (2.9)	
Death at 3 mo, n (%)			
No	123 (89.8)	170 (97.1)	0.024
Yes	14 (10.2)	5 (2.9)	

Abbreviations: CA = carotid artery; EVT = endovascular therapy; IVT = IV thrombolysis; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; sICH = symptomatic intracranial hemorrhage.
Values are number (percent) or median (interquartile range) as appropriate. The *p* values calculated by χ^2 and Mann-Whitney tests as appropriate.

Regarding safety outcomes, a larger proportion of patients were dead at 3 months in the EVT than in the IVT group, and this difference almost reached statistical significance (9.3% vs 2.8%; adjusted OR 3.75, 95% CI 0.97–14.54; $p = 0.06$; table 4). No other variables were associated with risk of death at 3 months in the multivariate regression model. sICH was rare in both groups (n = 3 in EVT vs n = 0 in patients with IVT), and the difference was not significant ($p = 0.997$).

Exploratory outcomes

We further tested the favorable outcome and risk of mortality between patients undergoing EVT alone (n = 53) vs IVT + EVT (n = 55) vs IVT alone (n = 108). Both the EVT and IVT + EVT procedures showed a nonsignificant difference in likelihood of reaching a favorable outcome at 3 months after stroke compared to IVT alone (OR 0.81, 95% CI 0.39–1.71, $p = 0.583$; and OR 1.08, 95% CI 0.51–2.29, $p = 0.831$, respectively). In contrast, the trend to a higher risk of death among patients with EVT compared to those with IVT was due largely to those undergoing EVT only (OR 12.75, 95% CI 2.36–68.74; $p = 0.004$) rather than IVT + EVT ($p = 0.990$). Indeed, none of the 13 deceased patients with EVT had undergone bridging therapy.

We identified 41 and 56 PS-matched pairs of patients with EVT ± IVT and patients with IVT only with either CA/M1 or M2 occlusions, respectively. For CA/M1 occlusions, patients with EVT had no difference in likelihood of reaching a favorable outcome at 3 months compared to patients with IVT only (OR 0.93, 95% CI 0.30–2.90; $p = 0.899$), as well as no increased risk of death ($p = 0.994$). Similarly, in patients with M2 occlusions, no significant associations were found between performing EVT or IVT only and favorable outcome (OR 1.12, 95% CI 0.41–2.99; $p = 0.821$) or death at 3 months (OR 1.36, 95% CI 0.165–11.25; $p = 0.774$).

Finally, we investigated whether the reperfusion grade could have influenced later functional outcome. mTICI scores were available only for patients undergoing EVT (reperfusers [mTICI score 2b and 3] n = 89, nonreperfusers [mTICI score 0, 1, and 2a] n = 17). The proportion of patients with EVT reaching a favorable outcome at 3 months was 66% among reperfusers and 46% among nonreperfusers, but this difference was not statistically significant (OR 2.04, 95% CI 0.61–6.86; $p = 0.247$). Similarly, we observed a mild reduction in mortality among reperfusers (7.8%) compared to nonreperfusers (17.6%), but this also did not reach statistical significance (OR 0.23, 95% CI 0.03–1.44; $p = 0.116$).

Discussion

This multicenter study found that in patients with acute ischemic stroke with LVO and mild neurologic symptoms (NIHSS score ≤5), EVT and IVT were similarly effective in

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Table 2 Baseline characteristics and outcome variables of PS-matched EVT- and IVT-treated patients

Variable	EVT (n = 108)	IVT (n = 108)	*p* Value
Age, y	69.7 (55.8–78.7)	68.7 (57.5–77.4)	0.682
Sex, n (%)			
F	55 (51)	58 (53.7)	0.785
M	53 (49)	50 (46.3)	
Prestroke mRS score, n (%)			
0	81 (75)	85 (78.7)	0.654
1	21 (19.4)	16 (14.8)	
2	6 (5.6)	7 (6.5)	
Hypertension, n (%)			
No	33 (31)	32 (29.6)	1.000
Yes	75 (69)	76 (70.4)	
Diabetes mellitus, n (%)			
No	96 (89)	88 (82.2)	0.233
Yes	12 (11)	19 (17.8)	
Hyperlipidemia, n (%)			
No	43 (39.8)	29 (26.9)	0.061
Yes	65 (60.2)	79 (73.1)	
Smoking, n (%)			
No	73 (67.6)	71 (65.7)	0.885
Yes	35 (32.4)	37 (34.3)	
Anticoagulant treatment, n (%)			
No	94 (87)	98 (90.7)	0.516
Yes	14 (13)	10 (9.3)	
NIHSS score (admission)	4 (2–5)	3 (2–5)	0.863
Occlusion site, n (%)			
CA	24 (22.2)	22 (20.4)	0.601
MCA (M1)	26 (24.1)	21 (19.4)	
MCA (M2)	58 (53.7)	65 (60.2)	
Onset-to-treatment time, h	3.32 (2.08–6.4)	1.95 (1.43–2.52)	<0.001
Reperfusion (mTICI score), n (%)			
0–2a	17 (16)		
2b–3	89 (84)		
sICH, n (%)			
No	105 (97.2)	108 (100)	0.242
Yes	3 (2.8)	0 (0)	
mRS score at 3 mo, n (%)			
0	35 (32.4)	32 (29.6)	0.313
1	33 (30.6)	39 (36.1)	
2	18 (16.7)	22 (20.4)	
3	6 (5.5)	8 (7.4)	
4	6 (5.5)	3 (2.8)	
5	0 (0)	1 (0.9)	
6	10 (9.3)	3 (2.8)	
Death at 3 mo, n (%)			
No	98 (90.7)	105 (97.2)	0.086
Yes	10 (9.3)	3 (2.8)	

Abbreviations: CA = carotid artery; EVT = endovascular therapy; IVT = IV thrombolysis; MCA = middle cerebral artery; mRS = modified Rankin Scale; mTICI = modified Thrombolysis in Cerebral Infarction Scale; NIHSS = NIH Stroke Scale; PS = propensity score; sICH = symptomatic intracranial hemorrhage.
Values are number (percent) or median (interquartile range) as appropriate. The *p* values estimated by χ^2 and Mann-Whitney tests as appropriate.

achieving a favorable functional outcome at 3 months. The EVT group showed a nonsignificant trend toward greater disability across the mRS range and nonsignificant higher mortality compared to the IVT group. The probability of survival with moderate to severe disability was low in both treatments.

The majority of patients with LVO and mild neurologic symptoms (NIHSS score ≤5) treated with EVT or IVT had a good clinical outcome; 63% after EVT and 65.7% after IVT maintained an mRS score of 0 to 1 at 3 months after the event. An even larger proportion of patients remained functionally independent (mRS score 0–2) at 3 months (79.7% with EVT and 86.1% with IVT). Our patients with LVO and low NIHSS score treated with EVT had better outcome than those reported in randomized trials of EVT for LVO (with mean NIHSS score 17), in which 26.9% and 46% of EVT-treated patients reached a favorable outcome and independence, respectively.[1] However, EVT-treated patients in our cohort had a slightly less favorable outcome compared to previous small observational studies focused on LVO-related AIS with minimal symptoms (mRS score 0–1 reported: 59%–62.5%),[10,14,19] while results are more in line with a recent retrospective observational study (55.7%).[16] Our results suggest that in patients with AIS with minimal symptoms, even in the presence of LVO, the potential benefits of an efficient acute recanalization with EVT compared to IVT may be less determinant for the final outcome. However, our study

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Table 3 Multivariable logistic regression models testing associations between type of treatment (EVT vs IVT) and both favorable outcome (mRS score 0–1) and independence (mRS score 0–2) at 3 months in PS-matched patients

	Favorable outcome at 3 mo		Independence at 3 mo	
Variables	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Treatment				
IVT	—	—	—	—
EVT	0.94 (0.51–1.72)	0.840	0.62 (0.28–1.37)	0.240
Age	0.99 (0.97–1.01)	0.47	0.94 (0.91–0.98)	0.004
Sex				
F	—	—	—	—
M	0.88 (0.46–1.68)	0.697	0.80 (0.34–1.88)	0.613
NIHSS score (admission)	0.89 (0.73–1.09)	0.252	1 (0.77–1.3)	0.988
Prestroke mRS score	0.3 (0.16–0.54)	0.001	0.44 (0.25–0.80)	0.007
Onset-to-treatment time	0.99 (0.96–1.03)	0.681	0.98 (0.95–1.01)	0.271
Occlusion site				
CA	—	—	—	—
MCA (M1)	1.01 (0.39–2.57)	0.985	2.42 (0.68–8.58)	0.169
MCA (M2)	1.12 (0.51–2.48)	0.771	1.25 (0.47–3.32)	0.652
Anticoagulation				
No	—	—	—	—
Yes	0.67 (0.26–1.77)	0.424	1.61 (0.45–5.81)	0.467

Abbreviations: CA = carotid artery; CI = confidence interval; EVT = endovascular therapy; IVT = IV thrombolysis; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; PS = propensity score.

does not allow defining subgroups of patients who may benefit from EVT compared to IVT alone, and we believe this important question should be addressed in an appropriately powered randomized controlled trial.

Our findings confirm that in patients with AIS with an NIHSS score ≤5 and LVO, IVT is effective and safe. In this study, IVT performed better in terms of favorable outcome than reported in randomized controlled trials of IVT not selected according to low NIHSS score or presence of LVO (≈35% of patients with mRS score 0–1).[9] Our results are in line with the recent randomized Potential of rtPA for Ischemic Stroke With Mild Symptoms (PRISMS) trial (AIS with NIHSS score ≤5 but included regardless of the presence of LVO), in which 78% of patients reached favorable outcome in the recombinant tissue plasminogen activator group (vs 81.5% in the placebo/aspirin group).[11] Our cohort treated with IVT showed a better outcome compared to a recent retrospective study on EVT in mild symptoms (54.4% favorable outcome), but comparison is hazardous because only 32.2% of the control group received IVT.[16] Our results may be somewhat surprising in that one might have expected a worse outcome in the IVT group due to the presence of LVO, a well-established marker of potential unfavorable outcome,[20,21] and clinical deterioration if not treated promptly with effective reperfusion therapy.[2,7,12] On the other hand, a low NIHSS score is also known to be a strong independent predictor of good outcome in LVO-associated AIS, even independently of collateral status.[2] One could speculate that this factor is more relevant than the presence of LVO. Nevertheless, in our study, we did not compare reperfusion therapies (EVT or IVT) vs a more conservative approach in this particular population.

EVT was associated with some safety aspects. Despite a good general outcome, there was a relatively higher rate of mortality (9.3% in EVT vs 2.8% in IVT alone; $p = 0.06$), although non-significantly different between the 2 groups and independent of age, prestroke mRS score, or NIHSS score at admission. However, the 3-month mortality in our EVT-treated population is still lower than reported in trials with LVO and higher NIHSS score: 15.3% as reported in a recent pooled analysis of EVT randomized controlled trials (mean NIHSS score 17)[1] and 26.5% as reported in a nonrandomized study of pure mechanical EVT in AIS with LVO (median NIHSS score 16).[22] Our mortality rate is more congruous with recent retrospective reports (8.9%)[16] and with a small case series of patients with a low NIHSS score, in which mortality in patients with EVT ranged from 6.2%[19] to 12%.[14]

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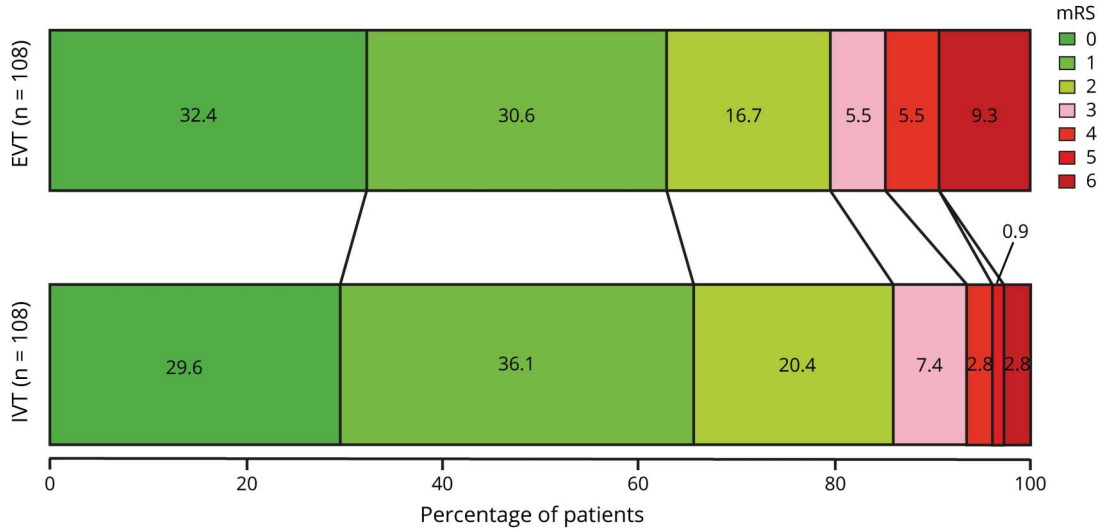
Figure Distribution of mRS scores at 3 months after stroke in propensity score–matched groups (EVT with or without IVT vs IVT alone)



proportion of patients with a favorable outcome at 3 months (modified Rankin Scale [mRS] score 0–1) was 63% among patients treated with endovascular therapy (EVT) and 65.7% in patients treated with IV thrombolysis (IVT). This difference was not statistically significant in the multivariate regression model adjusted for age, sex, baseline NIH Stroke Scale score, prestroke mRS score, time between stroke and treatment initiation, vessel occlusion, and prestroke anticoagulation therapy (odds ratio 1.09, 95% confidence interval 0.67–1.78; $p = 0.717$).

Mortality was not driven by sICH. sICH was a rare event in our study population, documented in no patients (0%) treated with IVT and 3 patients treated with EVT (2.8%). Despite the small number of events, we observed a lower proportion of sICH in IVT compared to the PRISMS study (3.2%), and the proportion of sICH in EVT-treated patients is lower than previously reported in patients with mild symptoms (range 4.4%–12%).[14,16,19] Mortality rate did not appear to be related to procedural complications of EVT, although we observed an increased risk of mortality among patients undergoing EVT without IVT (direct thrombectomy). In accordance with recent observations in IVT-ineligible patients treated with direct EVT,[23] we considered some potential associated unfavorable variables (time to treatment and pretreatment anticoagulation) in our multivariate regression model. Nevertheless, we postulate that IVT ineligibility may be intrinsically associated with some additional individual unfavorable factors that are difficult to appreciate in statistical analyses.

We performed several analyses to address whether our findings may be due in part to a bias toward more favorable characteristics among patients treated with IVT. In the unmatched comparison, we found a higher proportion of the more distal (M2) lesions in the IVT population. We corrected this by adopting first a PS-matching analysis that greatly limited this discrepancy. We corrected remaining imbalances between the 2 groups using multivariate regression models. In the adjusted comparison of the matched study groups, the differences in outcomes were independent of demographics, stroke severity (NIHSS score), occlusion site, onset-to-treatment time, and pretreatment anticoagulation. According to a recent meta-analysis based on the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium[24] and recent observations[16] indicating a nonsignificant trend toward higher efficacy of EVT vs IVT alone for CA and proximal M1 occlusion compared to more distal vessels (distal M1 and M2), we also performed a subgroup analysis based on vessel occlusion site. The primary and secondary outcomes did not differ comparing EVT vs IVT alone in all matched subgroup populations of patients. Finally, we observed trends toward greater chances of reaching a favorable outcome and survival among reperfused patients with EVT. Differences did not reach statistical significance, but we believe that this analysis was limited by the small number of nonreperfusers.

There are several differences between this and earlier studies assessing the effect of reperfusion therapy in patients with LVO and mild symptoms. First, to the best our knowledge, this is the first multicenter large-scale study that directly compares EVT and IVT in patients with LVO and mild neurologic deficits (NIHSS score ≤5). Second, this is the first study to use a PS-matching method in the primary analysis. In absence of data from randomized controlled trials (that excluded patients with NIHSS score <6)[1] and taking into account the difficulties encountered in patient recruitment in randomized trials of strokes with mild symptoms,[11] completing a randomized trial of EVT vs IVT would be challenging. PS matching of observational data provides the best evidence available to date to compare the safety and efficacy of EVT vs IVT in this particular population. Third, our results used high-quality standardized and prospectively collected data from a homogeneous cohort of consecutive patients with stroke.

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Table 4 Multivariable ordinal and logistic regression models testing associations between type of treatment (EVT vs IVT) and mRS score shift, survival with disability (mRS score 4–5), and death (mRS score 6) at 3 months

	mRS score shift at 3 mo		Disability at 3 mo		Death at 3 mo	
Variables	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Treatment						
IVT	—	—	—	—	—	—
EVT	1.09 (0.67–1.78)	0.717	1.77 (0.44–7.01)	0.419	3.75 (0.97–14.54)	0.06
Age	1.01 (0.99–1.03)	0.145	1.01 (0.95–1.07)	0.724	1.04 (0.98–1.10)	0.151
Sex						
F	—	—	—	—	—	—
M	1.06 (0.63–1.78)	0.821	0.76 (0.18–3.23)	0.71	0.89 (0.25–3.14)	0.854
NIHSS score (admission)	1.14 (0.97–1.35)	0.119	1.29 (0.78–2.12)	0.316	1.11 (0.75–1.65)	0.586
Prestroke mRS score	2.35 (1.51–3.66)	<0.001	2.75 (1.05–7.17)	0.039	1.53 (0.61–3.88)	0.364
Onset-to-treatment time	1.01 (0.99–1.03)	0.502	1 (0.95–1.05)	0.986	1.01 (0.96–1.07)	0.624
Occlusion site						
CA	—	—	—	—	—	—
MCA (M1)	0.49 (0.22–1.08)	0.078	0.18 (0.01–2.23)	0.182	0.57 (0.10–3.09)	0.513
MCA (M2)	0.85 (0.45–1.6)	0.614	0.51 (0.11–2.41)	0.399	0.52 (0.13–2.11)	0.357
Anticoagulation						
No	—	—	—	—	—	—
Yes	1.05 (0.47–2.33)	0.905	1.41 (0.21–9.46)	0.724	0.33 (0.31–3.43)	0.352

Abbreviations: CA = carotid artery; CI = confidence interval; EVT = endovascular therapy; IVT = IV thrombolysis; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.
All models adjusted for covariates of interest.

Our study has some limitations. Despite the matching and adjusting procedure, this study is not a randomized trial, and we cannot exclude the presence of additional confounding factors (other than those used to build PSs), potentially influencing both treatment choice and outcomes. In addition, even after PS matching, patients with EVT still had a larger interval between onset of symptoms and treatment than patients treated with IVT only. This was inevitable given the different time windows to perform IVT and EVT, and we attempted to overcome this issue by further adjusting all regression models including time to treatment as a covariate in the model. A control group (i.e., under best treatment without EVT or IVT) was not included in the study. Finally, we have no information on radiologic outcomes in terms of vessel recanalization in patients with IVT because follow-up vessel imaging is not routinely performed after IVT. This pragmatic study did not include perfusion imaging and ischemic core evaluation because they are not routinely performed to select patients for IVT in the standard treatment window. This approach may be warranted in more detailed future trials specifically addressing perfusion patterns and response to treatment in the late time window.

In patients with acute stroke with LVO and mild neurologic symptoms, EVT and IVT appear similarly effective for achieving a favorable functional outcome at 3 months, with a potentially increased risk of mortality observed in patients undergoing EVT alone. Our study is relevant for the ongoing debate concerning the suitability of EVT as optimal treatment for AIS with LVO and mild deficits and supports the need for further research to evaluate whether certain subgroups of patients with LVO and mild symptoms benefit from EVT.

Author contributions

The study was designed by C. Cereda (principal investigator). C. Manno, G. Disanto, Cereda, C. Manno, G. Bianco, C. Staedler, and C. Cereda analyzed and interpreted data. C. Manno, G. Bianco, G. Disanto, and C. Cereda drafted the manuscript. L. Bonati is the coordinator of the Swiss Stroke Registry. All authors made critical revisions.

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who contributed to the study design and/or provided data but did not participate in the analysis or writing of the report. They thank Melanie Price Hirt for English language correction and editing.

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Disclosure

C. Manno, G. Disanto, G. Bianco, S. Nannoni, M. Heldner, S. Jung, M. Arnold, J. Kaesmacher, M. Müller, S. Thilemann, H. Gensicke, E. Carrera, U. Fischer, T. Kahles, A. Luft, K. Nedeltchev, C. Staedler, and A. Cianfoni report no disclosures relevant to the manuscript. G. Kägi discloses honoraria from travel and advisory board fees from Bayer, Boehringer Ingelheim, and Zambon and research grants from the Swiss Heart Foundation, Swiss Parkinson Foundation, and Swiss National Science Foundation. L. Bonati received an unrestricted research grant from AstraZeneca and consultancy or advisory board fees or speaker's honoraria from Amgen, Bayer, Bristol-Myers Squibb, and Claret Medical, as well as travel grants from Amgen and Bayer. P. Michel reports no disclosures relevant to the manuscript. C. Cereda discloses consulting fees from Bayer, Bristol Myers Squibb, and Boehringer Ingelheim. Go to Neurology.org/N for full disclosures.

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Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms

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CORRECTIONS

Neurologic aspects of sweating and its disorders

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008730

In the Clinical Implications of Neuroscience Research article "Neurologic aspects of sweating and its disorders" by Minota et al.,[1] the Disclosure should have noted the grant support received from the NIH (R01 NS092625). The authors regret the error.

Reference

1. Minota K, Coon EA, Benarroch EE. Neurologic aspects of sweating and its disorders. Neurology 2019;92:999–1005.

Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008829

In the article "Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms" by Manno et al.,[1] Dr. Heldner's byline should read Mirjam R. Heldner, MD. The authors regret the error.

Reference

1. Manno C, Disanto G, Bianco G, et al. Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms. Neurology 2019;93:e1618–e1626.

Amyloid and cerebrovascular burden divergently influence brain functional network changes over time

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In the article "Amyloid and cerebrovascular burden divergently influence brain functional network changes over time" by Chong et al.,[1] the label beside the blue line in panel A of figure 2 should have read "svMCI PiB-." The authors regret the error.

Reference

1. Chong JSX, Jang H, Kim HJ, et al. Amyloid and cerebrovascular burden divergently influence brain functional network changes over time. Neurology 2019;93:e1514–e1525.

Child Neurology: Andersen-Tawil syndrome

Neurology® 2020;94:187. doi:10.1212/WNL.0000000000008828

Two images of patients in the article "Child Neurology: Andersen-Tawil syndrome" by Almuqbil and Srour,[1] published online March 16, 2015, have been removed because the patients requested that their consent for publication be withdrawn. The removal of the images does not invalidate the paper because an extensive verbal description of the patients was included within the text of the article. The American Academy of Neurology, who owns copyright of the article, the Editor of the journal, and the authors agreed that the images were unnecessary to the message of the paper and agreed to honor the request to remove them.

Reference

1. Almuqbil M, Srour M. Child Neurology: Andersen-Tawil syndrome. Neurology 2015;84:e78–e80.

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