This article has been accepted for publication in JNIS following peer review.

The definitive copyedited, typeset version is available online at 10.1136/jnis-2023-020411

Endovascular Therapy In Acute Ischemic Stroke With Poor Reperfusion Is Associated With Worse Outcomes Compared to Best Medical Management: A HERMES Substudy

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Number of tables: 2

Number of figures: 2

Supplementary material: 2 supplementary tables

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ABSTRACT

Background

We compared functional outcomes in acute ischemic stroke (AIS) patients with large vessel occlusion (LVO) undergoing endovascular treatment (EVT) with poor reperfusion to AIS-LVO patients treated with best medical management only.

Methods

Data are from the HERMES collaboration, a patient-level meta-analysis of seven randomized EVT trials. Baseline characteristics and functional outcomes (modified Rankin score at 90 days) were compared between patients with poor reperfusion (defined as modified Thrombolysis in Cerebral Infarction Score 0-1 on the final intracranial angiography run as assessed by the central imaging core lab) and patients in the control arm with multivariable logistic ordinal logistic regression adjusted for pre-specified baseline variables.

Results

Nine-hundred-seventy-two out of 1764 HERMES patients were included in the analysis: 893 in the control arm and 79 in the EVT arm with final mTICI 0-1. Poor reperfusion EVT patients had higher baseline National Institutes of Health Stroke Scale (median 19 [interquartile range: 15.5-21] vs 17[13-21], p=0.011). Poor reperfusion EVT patients had worse mRS at 90 days compared to control arm patients in adjusted analysis (median 4 [IQR3-6] vs. median 4[IQR 2-5], adjusted common odds ratio 0.59 [95%CI:0.38-0.91]). Symptomatic intracranial hemorrhage was not different between groups (3.9% vs 3.5%, p=0.75, adjusted odds ratio 0.94, [95%CI:0.23-3.88]).

Conclusion

Poor reperfusion after EVT was associated with worse outcomes than best medical management, although no difference in symptomatic intracranial hemorrhage was seen. These results emphasize the need for additional efforts to further improve technical EVT success rates.

What is already known on this topic

The substantial benefit of EVT has been demonstrated in various patient populations. Additionally, it has been shown that those patients undergoing EVT with unsuccessful (0-2a) reperfusion have equivocal outcomes as those receiving best medical management.

What this study adds

This study quantifies the difference in outcome between those with failed reperfusion (mTICI 0-1) and LVO patients receiving best medical management.

How this study might affect research, practice or policy

Our results show exceedingly poor outcomes in patients with failed reperfusion, emphasizing the need for improving technical EVT success rates.

INTRODUCTION

The goal when treating acute ischemic stroke (AIS) due to large vessel occlusion (LVO) is tissue reperfusion via vessel recanalization. Until several years ago, intravenous thrombolysis (IVT) was the only available treatment option to do so. In 2015 however, endovascular thrombectomy (EVT) was proven to be more effective in recanalizing LVO compared to best medical management, including IVT[1]. Shortly thereafter, EVT has become standard of care for AIS patients with LVO presenting within 24 hours from onset and limited ischemic changes on baseline imaging, with a number needed to treat of ~2.5[1]. Since then, additional EVT trials have continued and continue to broaden EVT eligibility criteria to include late-presenting patients, those with large ischemic core at baseline, and there are ongoing trials for EVT in more distal occlusions [2, 3, 4, 5, 6]. However, EVT is not without risks, and successful reperfusion cannot always be achieved. Successful reperfusion, defined as antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (modified thrombolysis in cerebral infarction score [mTICI] 2b-3), used to occur in only 70% of EVT cases[1], although recent trials report rates closer to 90%[7]. While previous studies have shown that patients undergoing EVT without successful reperfusion do not have worse clinical outcomes compared to those treated with best medical management[7], these studies included patients with partial reperfusion (ie, some degree of reperfusion but <50%, mTICI 2a). How outcomes of patients with poor reperfusion (ie, final mTICI 0 or 1) compare to patients treated with best medical management has not been well studied.

The aim of this study was therefore to investigate the association of EVT on clinical outcome in patients with poor reperfusion, defined as mTICI of 0-1.

METHODS

Study Design / Study Cohort

The HERMES (Highly Effective Reperfusion Using Multiple Endovascular Stroke Trials) collaboration is a prospective patient level meta-analysis of 7 randomized controlled trials that evaluated the benefit of EVT over and beyond best medical management: the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands)[8], the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times)[9], the EXTEND-IA trial (Extending the Time for Thrombolysis in Emergency Neurologic Deficits-Intra-Arterial)[10], the SWIFT PRIME trial (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment)[11], the REVASCAT trial (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Either Hours of Symptom Onset)[12], the PISTE trial (Pragmatic Ischemic Thrombectomy Evaluation)[13], and the THRACE trial (Trial and Cost-Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke)[14]. The details of the HERMES patient sample and search strategy have been previously reported[1, 15]. In brief, the original investigators searched PubMed for randomized controlled trials comparing EVT to standard of care medical therapy from 2010 to 2017, with the resulting meta-analysis being a post-hoc analysis of individual patient data. Patient consent was obtained in each of the trials prior to enrolment, unless the presiding ethics board allowed for deferral of consent.

The primary objective of the current study was to evaluate differences in clinical outcomes in patients undergoing EVT with poor reperfusion (defined as mTICI 0-1) could be achieved vs. control arm patients, who were treated with best medical management, including intravenous alteplase if indicated. To control for the potential early reperfusion due to intravenous alteplase use in the control group, we performed additional subgroup analyses a) including only patients that did not show indications of early neurological improvement post-thrombolysis (whereby early neurological improvement was used as a proxy for early reperfusion), and b) only including patients that did not receive alteplase. We deliberately defined “poor reperfusion” as mTICI 0-1 in order to avoid any potentially confounding effects from the restoration of partial blood flow that could occur in patients with final mTICI score of 2a. mTICI scores were assessed by a central imaging core lab that was blinded to clinical outcomes.

Ethics Approval

The HERMES trial is a meta-analysis of seven randomized control trials that each received IRB/ethics committee approval at their respective institutions, approval was not needed for the conglomoration of patient data, per the original publication in Lancet.

Outcome measures

The primary outcome measure was functional outcome across the modified Rankin Scale (mRS) at 90 days (mRS shift analysis). Secondary outcomes included different dichotomizations of the mRS, namely excellent (mRS 0-1), good (mRS 0-2), and poor (mRS 5-6) functional outcome at 90 days, as well as early neurological improvement (ENI, defined as an improvement in National Institutes of Health Stroke Scale (NIHSS) of at least 10 points compared to baseline in the first 24 hours), change in NIHSS at 24 hours compared to baseline, and final infarct volume as measured on 24h CT or MRI. Safety outcomes were mortality at 90 days, symptomatic intracranial hemorrhage (sICH, as defined in each constituent trial), and space occupying parenchymatous hematoma exceeding 30% of the infarct volume (PH2 according to the Heidelberg Bleeding Classification) at 24 hours[16].

Statistical Analysis

We compared baseline, imaging, and procedural (where relevant) characteristics of patients who underwent unsuccessful reperfusion to those of patients in the control arm using standard descriptive statistics as appropriate.

For adjusted analysis, ordinal logistic regression was used for the primary outcome (ordinal mRS/mRS shift analysis) and change in NIHSS at 24 hours compared to baseline, and binary logistic regression was used for binary outcomes (mRS 0-1, mRS 0-2, mRS 5-6, mortality, ENI, PH2 at 24 hours, and sICH at 24 hours). Notably, 90-day mRS was not available for 21 subjects in the HERMES meta-analysis, of which 16 were in the control group and 1 was in the mTICI 0-1 group. These patients were included in the baseline characteristics section, but not the associated grotto bars. Analyses were adjusted for the following pre-specified baseline characteristics: age, sex, NIHSS, Alberta Stroke Program Early CT Score (ASPECTS), occlusion location (terminal internal carotid artery vs. M1 segment of the middle cerebral artery vs. M2 segment of the middle cerebral artery), alteplase treatment, and time from onset to randomization. Missing data were minimal and thus not imputed; only available data were used for the analysis.

We performed sensitivity analysis on two subgroups: first, we excluded patients with clinical signs of early recanalization in the control group, defined as NIHSS 0-2 at 24 hours[17]. Second, we considered only patients that did not receive intravenous alteplase in the control group. For the purpose of this study, we defined early neurological improvement as an improvement in National Institutes of Health Stroke Scale (NIHSS) at 24 hours of at least 10 points compared to baseline. The rationale behind excluding those patients from the control arm was that we were interested in comparing those patients in the control arm without recanalization to patients with failed EVT, and we used a) the presence of early neurological improvement and b) treatment with intravenous alteplase as proxies for recanalization in the sensitivity analyses, since control arm patients with ENI and control arm patients receiving intravenous alteplase are

more likely to recanalize. A supplementary table with outcomes of patients that achieved mTICI 0-2a is included for reference.

Statistical analyses performed with SAS software, version 9.4 (SAS Institute, Cary, NC) and R, version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Data Availability Statement

Data from this study are available from the corresponding author and after approval by the HERMES executive committee upon reasonable request.

RESULTS

Out of the 1764 patients included in the HERMES meta-analysis, 972 patients were included in this study (893 in the control arm and 79 in the EVT arm with final mTICI 0-1). Of note, not all variables were available for all patients (**Figure 1**). The EVT group was much smaller than the control group because EVT resulted in some degree of reperfusion (ie, final mTICI 2a or greater) in most cases. **Table 1** compares the baseline characteristics of the two groups. Except for the baseline NIHSS, which was higher in the EVT patients with poor reperfusion (median 19 [interquartile range 15.5-21] vs. median 17 [13-21], respectively, P = 0.011), no differences in baseline variables were seen (**Table 1**).

Table 1. Baseline characteristics of EVT patients with poor reperfusion vs. control arm patients

Characteristic	**EVT with final mTICI 0/1 (n=79)** Mean ± SD (N) [Median] (IQR) or % (n/N)	**Best medical management (n=893)** Mean ± SD (N) [Median] (IQR) or % (n/N)	**p-value**
Age (years)	65.2 ± 13.3 (79) [64.0] (54.1,75.5)	65.7 ± 13.5 (890) [67.8] (58.0,76.0)	0.589
Female	40.5% (32/79)	47.3% (421/891)	0.401
Systolic blood pressure (mmHG)	147.7 ± 24.4 (79) [150.0] (132.0,166.0)	145.3 ± 24.5 (886) [144.0] (129.0,161.0)	0.400
Diabetes mellitus	11.4% (9/79)	17.5% (156/889)	0.211
Hypertension	48.1% (38/79)	58.8% (523/890)	0.075
Atrial fibrillation	34.0% (18/53)	32.6% (223/684)	0.879
Prior stroke	14.1% (11/78)	10.3% (92/889)	0.210
Hyperlipidemia	34.7% (26/75)	40.2% (351/873)	0.161
Glucose (mg/dl)	129.1 ± 34.9 (79) [125.5] (106.4,145.8)	130.1 ± 57.8 (863) [120.0] (103.6,140.4)	0.276

NIHSS at baseline*	18.4 ± 4.6 (79) [19.0] (15.5,21.0)	16.9 ± 5.3 (887) [17.0] (13.0,21.0)	0.011
ASPECTS at baseline	7.1 ± 2.0 (77) [7.0] (6.0,8.0)	7.5 ± 2.0 (876) [8.0] (7.0,9.0)	0.057
tPA delivered	94.9% (75/79)	90.6% (809/893)	0.303
Occlusion location			0.806
ICA	31.5% (23/73)	27.4% (227/829)	
M1	63.0% (46/73)	64.8% (537/829)	
M2	5.5% (4/73)	7.7% (64/829)	
Collateral grade			0.262
0	1.8% (1/55)	1.2% (8/651)	
1	25.5% (14/55)	16.6% (108/651)	
2	43.6% (24/55)	42.2% (275/651)	
3	29.1% (16/55)	39.9% (260/651)	
Onset to randomization	204.8 ± 69.7 (79) [197.0] (146.5,247.0)	201.8 ± 84.9 (889) [184.0] (140.0,250.0)	0.327
Onset to alteplase administration	120.8 ± 49.0 (74) [116.5] (77.0,154.5)	127.9 ± 59.9 (809) [120.0] (85.0,161.0)	0.506
Onset to puncture	265.8 ± 72.9 (73) [270.0] (210.0,315.0)	NA	NA
*Statistically significant difference Abbreviations: EVT: endovascular treatment; mTICI: modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; tPA, tissue plasminogen activator; ICA, Internal Carotid Artery			

Note that not all baseline characteristics and treatment/workflow variables were available for all patients; hence, the denominator is smaller than the overall number of patients with failed EVT/the overall number of control arm patients in some cells.

Outcomes in EVT patients with poor reperfusion vs. control arm patients

Primary outcome data were available for all included patients (**Table 2**). mRS at 90 days was worse in the poor reperfusion EVT group than in the control arm (median 4 [IQR 3-6] vs. median 4 [IQR 2-5]). In the adjusted analysis EVT without successful reperfusion was associated with worse ordinal mRS at 90 days compared to best medical management (aOR 0.59, 95% CI 0.38-0.91, **Table 2**). **Table 2** also compares secondary and safety outcomes in EVT patients with poor reperfusion vs. control arm patients. Poor reperfusion after EVT was associated with lower chances of achieving excellent outcome (mRS 0-1 at 90 days: aOR 0.26[95% CI: 0.07-0.98]), higher risk of poor outcome (mRS 5-6 at 90 days, aOR 1.72[95%CI 1.00-2.94]), higher risk of death at 90 days (aOR 2.46 [95% CI 1.42-4.27]), were less likely to show ENI (aOR 0.39 [95% CI

0.18-0.83]) and showed less changes on the NIHSS between 24h and baseline (acOR 3.0 [95% CI 1.49-4.51]). For mRS 0-2 and the other secondary and safety outcomes, no differences were seen.

Table 2: Primary, secondary and safety outcomes in EVT patients with poor reperfusion vs. control arm patients.

Outcome	EVT mTICI 0-1 median (IQR) or % (n/N) or mean ± SD	CTL median (IQR) or % (n/N) or mean ± SD	aOR/acOR or beta	LCL	UCL	p-value
mRS (ordinal) at 90 days	4 (3, 6)	4 (2, 5)	0.59	0.38	0.91	0.0160
mRS 0-1 at 90 days	3.8% (3/78)	16.6% (146/877)	0.26	0.07	0.98	0.0471
mRS 0-2 at 90 days	21.8% (17/78)	30.6% (268/877)	0.82	0.42	1.60	0.5573
mRS 5-6 at 90 days	41.0% (32/78)	28.7% (252/877)	1.72	1.00	2.94	0.0496
Mortality at 90 days	34.2% (27/79)	17.3% (153/884)	2.46	1.42	4.27	0.0014
Early neurological improvement	10.4% (8/77)	23.8% (204/857)	0.39	0.18	0.83	0.0156
PH2 at 24h	2.6% (2/77)	4.8% (42/874)	0.42	0.10	1.80	0.2408
Symptomatic ICH at 24h	3.9% (3/76)	3.5% (31/877)	0.94	0.23	3.88	0.9352
Change in NIHSS at 24h	0.11 ± 6.49	-3.16 ± 6.69	3.00	1.49	4.51	0.0001
Final infarct volume	172.09 ± 144.72	93.74 ± 105.58	57.00	28.78	85.22	<0.0001

Abbreviations: EVT: endovascular treatment; mTICI: modified Thrombolysis in Cerebral Infarction; aOR, adjusted odds ratio; acOR, adjusted common odds ratio; LCL, lower confidence limit; UCL, upper confidence limit; mRS, modified Rankin Scale; ENI, early neurological improvement; PH2, parenchymal hematoma, type 2; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale

Sensitivity Analyses

Two sensitivity analyses were performed; one in which patients with early neurological improvement in the control group were excluded, and one in which patients who received intravenous alteplase in the control group were excluded. In sensitivity analysis 1, only a small fraction of the original control cohort (n=103, 12%) showed early neurological improvement and were therefore excluded. Exclusion of these patients yielded similar effect size estimates, although the differences in ordinal mRS, excellent outcome and ENI did not achieve statistical significance (**Suppl. Table 1**). After excluding patients who received intravenous alteplase, few

patients were left for the analysis, which yielded similar effect size estimates compared to the main analysis, although due to the low sample size, only the association of EVT with poor reperfusion and mortality and change between 24 hour and baseline NIHSS remained significant (**Suppl. Table 2**). Grotta bars for the primary and two sensitivity analyses can be found in **Figure 2**. Outcomes for the cohort of patients in the EVT group that achieved mTICI 0-2a were slightly better than the mTICI 0-1 group, although similarly many failed to reach statistical significance (**Suppl. Table 3**).

DISCUSSION

We found that EVT patients with failed reperfusion following EVT had significantly worse outcomes compared to patients not undergoing EVT. Sensitivity analyses, in which only patients without early neurological improvement and those without intravenous alteplase treatment were included in the control arm showed similar results, albeit not always statistically significant.

Overall, our results indicate that patients with failed EVT fare worse than those receiving best medical management. This is consistent with prior publications who suggest that patients with final mTICI 0 (ie, lack of any reperfusion on the final angiogram) show worse outcomes that those treated with best medical management[7, 18].

Baseline factors that could – at least partially- explain such outcome differences include onset to treatment time, baseline ASPECTS, procedural complications and baseline clinical status. However, the two groups in this study had similar baseline characteristics, except for baseline NIHSS, which was slightly higher in EVT patients with poor reperfusion. Of note, the fact that the differences in outcome persisted in adjusted analysis suggests that the baseline NIHSS alone does not explain the worse prognosis of EVT patients with poor reperfusion.

The reasons for failed reperfusion are manifold and include procedural difficulties due to clot characteristics (age, organization, location, embolic vs. non embolic), vessel tortuosity, and other patient-specific anatomical challenges[19]. Indeed, these factors have been shown to be associated with poor reperfusion and poor outcomes[20]. Furthermore, both time to revascularization[21] and number of retrieval attempts has been shown to be associated with failed reperfusion and worse clinical outcome[22, 23]. [24] Repeated contrast injections and workflow-related factors are other potential explanations. Since the HERMES collaboration did not capture detailed information on vascular anatomy, procedural characteristics and complications, we were unable to assess these factors in detail. [25]

Another potential explanation for worse outcomes in EVT patients with poor reperfusion is endovascular damage created by mechanical manipulation and subsequent vessel wall injury during the procedure. Although studies have shown iatrogenic endothelial injury occurs during EVT, its clinical significance is uncertain, and since no histological specimens were available, we

were unable to confirm or refute this hypothesis[26, 27]. The results of this study suggest that EVT may cause clinically significant damage, but this damage is masked when partial reperfusion is achieved.

Hemorrhage alone is unlikely to explain the worse outcomes in patients with failed reperfusion in this study, since sICH prevalence in those receiving EVT with poor reperfusion versus those receiving best medical management did not significantly differ. [28]

In summary, we observed clearly worse outcomes in EVT patients with poor reperfusion compared to those receiving best medical management, and the underlying reasons for this difference can neither be explained by baseline characteristics nor by intracranial hemorrhage. Procedural complications and EVT-induced vessel wall injury could potentially explain the observed differences, although this cannot be proven in the current study due to lack of detailed procedural information and histological specimens. One retrospective study has indicated that baseline NIHSS, low number of EVT attempts, stroke etiology and less infarct growth between baseline and 24 hours may be predictors of favorable outcomes in patients with failed EVT[18]. But ultimately, the reasons for the harm of failed EVT, reliable markers to prospectively identify patients at high-risk of such harm, and potential strategies to mitigate the harmful effects of failed reperfusion, eg, through rescue maneuvers or neuroprotective drugs, will need to be investigated in future research.

Limitations

This study has several limitations besides the lack of detailed procedural information and histological specimens. The different trials had slightly different inclusion and exclusion criteria and core lab imaging definitions, which introduces some heterogeneity. Moreover, since the HERMES trials have been performed, there have been improvements in devices and clinician experience over time, which has probably led to improved reperfusion rates and may have reduced procedural complications, and the results may look different if the study were to be repeated today. Confounding factors such as stroke etiology and procedural complications may have influenced our results as well, and the limited number of patients with failed EVT may limit the reliability of our results. Lastly, the HERMES dataset also included only patients treated in comprehensive stroke centers and thus may lack generalizability to the entire stroke patient population.

Conclusions

Poor reperfusion after EVT was associated with worse outcomes compared to best medical management. While the reasons for these differences remain unclear, our results emphasize the need for additional efforts to further improve technical EVT success rates.

Acknowledgements: None

Funding: None

Contributorship Statement: Nathaniel Rex, Scott Brown, Johanna Ospel: Conceptualization, literature search, drafting and critical revision of the manuscript and figures. Mayank Goyal: Conceptualization, critical revision of the manuscript and figures. Remaining authors: critical revision of the manuscript.

Disclosures:

Nathaniel Rex has nothing to disclose.

Johanna Ospel received consulting fees from Nicolab.

Scott Brown receives support from the University of Calgary and is on the data safety and monitoring advisory board of the TESLA study.

Rosalie McDonough is a shareholder of Collavidence Inc.

Nima Kashani has nothing to disclose.

Michael Hill received support from Medtronic LLC via a grant to the University of Calgary for the HERMES collaboration (now complete and inactive). He reports additional support from Boehringer-Ingelheim to the University of Calgary for the TEMPO-2 trial, from Biogen Inc. to the University of Calgary, and from NoNo Inc to the University of Calgary for the ESCAPE-NA1 trial and the ESCAPE-NEXT trial, as well as money from the Canadian Institutes for Health Research for the ESCAPE-NA1 and ESCAPE-NEXT trials, as well as from Alberta Innovates to the University of Calgary for the QuICR Alberta Stroke Program for the ESCAPE-NA1 trial. He additionally reports paid work for the adjudication of clinical trial outcomes from Sun Pharma and Brainsgate Inc. He is on the data safety monitoring board for RACECAT trial, Oncovir Hiltonel trial, DUMAS trial, ARTESIA trial, and BRAIN-AF trial. He is the president of the Canadian Neurological Sciences Federation and Canadian Stroke Consortium. He has private stocks in Circle Inc and PureWeb Inc.

Diederik Dippel has nothing to disclose.

Bruce Campbell has nothing to disclose.

Keith Muir has received grants from the British Heart Foundation, The Stroke Association, and Innovate UK for the ATTEST-2 and TEMPO-2 trials. He has accepted consulting fees from Boehringer-Ingelheim, Abbvie, and Biogen Inc. He has received lecture fees from Boehringer Ingelheim. He is on the data safety and monitoring board of the ARREST trial.

Andrew Demchuk has nothing to disclose.

Serge Bracard has nothing to disclose.

Francis Guillemin has nothing to disclose.

Tudor Jovin has nothing to disclose.

Peter Mitchel has received royalties or licenses from Medtronic and Stryker for institutional research support, and support from Stryker, Medtronic, and Microvention for attending meetings and/or travel.

Philip White has nothing to disclose.

Jeffrey Saver has nothing to disclose.

Mayank Goyal has received grants from NoNo Inc, Medtronic, and Cerenovus via the University of Calgary. He has received royalties or licenses from GE Healthcare and Microvention. He has received consulting fees from Microvention, Medtronic, Stryker, and Mentice. He has stock or stock options in Circle Neurovascular.

FIGURES

Figure 1: Flowchart of the HERMES study that shows trial population information as well as data availability by outcome for the primary analysis.

Figure 2: Modified Rankin Score of EVT patients with poor reperfusion (final mTICI0/1) that underwent EVT vs. best medical management. (A) shows the entire sample, (B) shows the sample after excluding intravenous alteplase patients, and (C) shows the sample after excluding patients with early neurological improvement. modified Rankin Scale; EVT: endovascular treatment; mTICI: modified Thrombolysis in Cerebral Infarction; ENI, early neurologic improvement. Note that there were 79 patients with final mTICI 0/1 in A-C as stated in Table 1, but mRS was missing in 1 of them. Also note that there were 84 patients without tPA in the control arm in (B), but mRS was missing for 4 patients. Lastly, note that there were 774 patients without early neurological improvement in (C), but mRS was missing for 7.

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