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Benjamin Gory, Stephanos Finitzis, Jean Marc Olivot, Sébastien Richard, Gaultier Marnat, et al.. Intravenous Thrombolysis before Complete Angiographic Reperfusion: Beyond Angiographic Assessment to Target Microvascular Obstruction?. *Annals of Neurology*, 2024, 95 (4), pp.762-773. <10.1002/ana.26867>. <hal-04626800>

HAL Id: hal-04626800

<https://hal.science/hal-04626800v1>

Submitted on 30 Aug 2024

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Intravenous Thrombolysis before Complete Angiographic Reperfusion: Beyond Angiographic Assessment to Target Microvascular Obstruction?

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Endovascular Treatment in Ischemic Stroke Registry Investigators

Objective: Recent data have suggested that ineffective tissue reperfusion despite successful angiographic reperfusion was partly responsible for unfavorable outcomes after endovascular therapy (EVT) and might be modulated by intravenous thrombolysis (IVT) use before EVT. To specifically decipher the effect played by IVT before EVT, we compared the clinical and safety outcomes of patients who experienced a complete reperfusion at the end of EVT according to IVT use before EVT.

Methods: The Endovascular Treatment in Ischemic Stroke (ETIS) registry is an ongoing, prospective, observational study at 21 centers that perform EVT in France. Patients were included if they had an anterior large vessel occlusion of the intracranial internal carotid artery or middle cerebral artery (M1/M2 segments) and complete reperfusion (expanded Thrombolysis in Cerebral Infarction score = 3) with EVT within 6 hours, between January 2015 and December 2021. The cohort was divided into two groups according to IVT use before EVT, and propensity score matching (PSM) was used to balance the two groups. Primary outcome was the shift in the degree of disability as measured by the modified Rankin Scale (mRS) at 90 days. Secondary outcomes included favorable outcome (mRS 0–2) at 90 days. Safety outcomes included symptomatic intracranial hemorrhage and 90-day mortality. Outcomes were estimated with multivariate logistic models adjusted for age, National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, and time from symptom onset to puncture.

Results: Among 5,429 patients included in the ETIS registry, 1,093 were included in the study, including 651 patients with complete recanalization treated with IVT before EVT. After PSM, 488 patients treated with IVT before EVT were

View this article online at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ana.26867). DOI: 10.1002/ana.26867

Received Aug 2, 2023, and in revised form Dec 19, 2023. Accepted for publication Dec 20, 2023.

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A list of the Endovascular Treatment in Ischemic Stroke Registry Investigators is provided in Appendix A.

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compared to 337 patients without IVT. In the matched cohort analysis, the IVT+EVT group had a favorable shift in the overall mRS score distribution (adjusted odds ratio [aOR] = 1.41, 95% confidence interval [CI] = 1.04–1.91, $p = 0.023$) and higher rates of favorable outcome (61.1% vs 48.7%, aOR = 1.49, 95% CI = 1.02–2.20, $p = 0.041$) at 90 days compared with the EVT alone group. Rates of symptomatic intracerebral hemorrhage were comparable between both groups (6.0% vs 4.3%, aOR = 1.16, 95% CI = 0.53–2.54, $p = 0.709$).

Interpretation: In clinical practice, even after complete angiographic reperfusion by EVT, prior IVT use improves clinical outcomes of patients without increasing bleeding risk.

ANN NEUROL 2024;95:762–773

Endovascular therapy (EVT), with or without prior intravenous thrombolysis (IVT), is the mainstay of treatment for acute ischemic stroke (AIS) due to an anterior circulation large vessel occlusion (LVO),^{1,2} with angiographic reperfusion rates now exceeding 80 to 90% at the end of procedure.³ However, several studies recently questioned the added value of IVT prior to EVT, especially given its relatively poor efficacy in terms of proximal artery recanalization,⁴ its higher risk of hemorrhagic transformations, thrombus fragmentation, and cost of the treatment in some countries.⁵ As such, several recent international randomized controlled trials have compared the efficacy and safety of IVT prior to EVT (IVT+EVT) versus EVT alone in stroke patients with LVO directly admitted to endovascular capable centers, but with conflicting results.^{6–11} Favorable outcomes were overall similar in the IVT+EVT and EVT groups, but patients who received IVT prior to EVT tended to experience a nonsignificantly better functional outcome than those who did not.^{5,12} In addition, a recent individual patient data meta-analysis (Improving Reperfusion Strategies in Ischemic Stroke)¹³ and a study-level meta-analysis published in the European Stroke guidelines reported significantly improved rates of final expanded Thrombolysis in Cerebral Infarction (eTICI) score in patients treated by lytic agents prior to EVT.¹⁴ However, as most patients randomized to the IVT+EVT group had persistent LVO at the beginning of EVT despite IVT use, these findings could suggest an additional effect played by IVT on microcirculation, especially during persistent LVO (ie, during patient's transfer or during EVT) and/or possibly after successful (but not complete) angiographic reperfusion by EVT (ie, especially for persistent or procedure-related distal medium vessel occlusions). Regarding microcirculation, the recent phase 2b randomized, double-blind, placebo-controlled CHOICE trial found that among AIS patients with LVO and successful EVT, the use of adjunct intra-arterial alteplase compared with placebo resulted in a greater likelihood of excellent neurological outcome at 90 days, thereby illustrating the effect of targeting downstream microvascular thrombosis on clinical outcome.¹⁵ In addition, extensive data reported that effective tissue reperfusion was a stronger predictor of good clinical outcome compared to recanalization.^{16–19} In light of

these recent data, we sought to decipher the effect played by IVT before EVT by comparing the clinical and safety outcomes of AIS patients with LVO for whom a complete recanalization was obtained at the end of EVT (ie, eTICI 3), according to IVT use before EVT. Our hypothesis was that, in a setting of complete angiographic reperfusion, patients treated with IVT before EVT would still have increased odds of functional outcomes at 90 days compared to patients treated with EVT alone.

Patients and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We used data from the Endovascular Treatment in Ischemic Stroke (ETIS) registry (NCT03776877), which is an ongoing, multicenter, prospective, observational study evaluating patients suffering from an AIS due to an anterior or posterior LVO treated with EVT at 21 comprehensive stroke centers in France. Data from the ETIS registry were collected and analyzed according to the recommendations of the “Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé.” Written informed consent was obtained from all patients or their legal representatives. Details regarding data collection and materials have been previously published.²⁰ As the present study is observational, adherence to the STROBE criteria was enforced.²¹

For the present study, inclusion criteria were as follows: (1) adult patients (≥ 18 years old) with an anterior LVO (intracranial carotid artery, M1 or M2 segment of the middle cerebral artery) treated by EVT between January 1, 2015 and December 31, 2021; (2) identical anterior LVO between the first angiographic run and the admission noninvasive imaging (ie, failure of proximal recanalization with IVT or physiologic fibrinolysis in the case of IVT contraindication); (3) complete angiographic reperfusion (ie, eTICI 3) with at least one pass of thrombectomy; and (4) time from onset to IVT ≤ 4.5 hours and time from onset to puncture ≤ 6 hours. Patients with tandem occlusions, use of intra-arterial

thrombolysis after EVT, posterior LVO, and intrahospital stroke, for whom IVT status was not known, and for whom EVT was not performed were excluded.

Data Collection and Clinical Definitions

Patients' clinical, radiological, and treatment characteristics were collected prospectively. Most patients preferentially underwent brain magnetic resonance imaging (MRI) at baseline or brain computed tomography (CT) scan with CT angiography in cases of MRI contraindication. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed on the baseline CT or diffusion-weighted imaging. Patients were treated in a dedicated neuroangiography suite with up-to-date equipment under conscious sedation or general anesthesia. First-line endovascular strategy included the use of last generation stent retrievers and/or thromboaspiration catheters. Successful and complete reperfusion were defined as an ϵ TICI score of 2b–3 and 3, respectively. Final ϵ TICI score was assessed by one neuroradiologist at each center (>10 years of experience), prospectively, blinded to the results of clinical outcome. Imaging follow-up was performed systematically 24 hours after EVT and also analyzed by one neuroradiologist (>10 years of experience) at each center blinded to the procedure and clinical outcome. Functional outcome was assessed with the modified Rankin Scale (mRS) at 90 days by certified neurologists or research nurses unaware of the initial treatment (ie, IVT) during face-to-face interviews or phone calls with the patient or their relatives.

Clinical and Imaging Outcomes

The primary efficacy outcome was the shift in the degree of disability as measured by the mRS at 90 days. Secondary efficacy outcomes included favorable outcome, defined as an mRS between 0 and 2 at 90 days, and excellent outcome defined as an mRS between 0 and 1 at 90 days. Early neurological improvement at 24 hours was defined as a National Institutes of Health Stroke Scale (NIHSS) score between 0 and 1 at 24 hours or a reduction of at least 8 points on the NIHSS. Additional efficacy outcomes were number of passes ≥ 2 and the time from puncture to successful angiographic reperfusion. Safety outcomes included parenchymal hematoma (PH; comprising PH 1 and PH 2, as previously published²²; symptomatic intracranial hemorrhage (sICH), defined as any PH on the 24-hour imaging associated with an increase of 4 points or more on the NIHSS within 24 hours attributable to the hemorrhage²³; and all-cause mortality at 90 days.

Statistical Analysis

Quantitative variables are expressed as the mean (standard deviation) for normally distributed parameters or median

(interquartile range) otherwise. Categorical variables are expressed as number (percentage). Patients were divided into two groups according to IVT use before EVT. Baseline characteristics were compared between these two groups using the Student *t* test for Gaussian continuous variables, Mann–Whitney *U* test for non-Gaussian continuous variables, or χ^2 test (or Fisher exact test when the expected cell frequency was <5) for categorical variables, as appropriate. To calculate the interrater agreement for differentiating ϵ TICI 3 from ϵ TICI 2c reperfusion, 3 raters with >5 years of experience in EVT independently rated 30 random cases from the study sample with equal proportions of occlusion locations and reperfusion grades, which allowed the calculation of a multirater kappa statistic.

To reduce the effects of potential confounding factors between group comparisons, we used propensity score methods.²⁴ The propensity score was used to assemble well-balanced groups (propensity score-matched cohort) and was estimated using a generalized linear mixed model with a binomial distribution and a logit link. The effect of the therapeutic approach was estimated using the inverse probability of treatment weighting propensity score method (using inverse propensity score as weight in univariable and multivariable logistic regression models). The propensity score for each individual was defined as the probability of being treated with IVT before EVT given the patient's age, hypertension, hypercholesterolemia, smoking, ischemic heart disease, anticoagulation, stroke etiology, history of prior stroke, prestroke mRS, admission mode (drip and ship, mothership), admission NIHSS and ASPECTS, general anesthesia, and time from symptom onset to puncture. Next, weights were calculated as the inverse of the propensity score and were applied to the study population to create a pseudopopulation in which confounders were equally distributed across exposed and unexposed groups. Comparisons in binary outcomes (early neurological improvement, favorable outcome, excellent outcome, 90-day all-cause mortality, and hemorrhagic complications) between groups were made using inverse propensity score-weighted logistic models, and odds ratios (ORs) were calculated. Comparison in the overall distribution of mRS (shift analysis) was performed with an inverse propensity score-weighted ordinal logistic model; common OR for 1-point improvement was derived from this model as effect size. Comparisons in outcomes were further adjusted for prespecified confounders (age, admission NIHSS and ASPECTS, time from symptom onset to groin puncture). Finally, we assessed heterogeneity of outcomes according to different subgroups: age (≤ 70 , >70 years), admission ASPECTS (≤ 6 , >6) and NIHSS (≤ 20 , >20), occlusion type (M1, M2, intracranial carotid artery), time from onset to

puncture (≤ 270 , >270 minutes), and number of passes (≤ 2 , >2), by including the corresponding interaction into the multivariable inverse propensity score-adjusted models. Effects are presented as ORs with 95% confidence intervals (CIs) and were calculated with univariable and multivariable logistic regression models adjusted for age, admission NIHSS, admission ASPECTS, and time from symptom onset to puncture. Missing demographic and procedural data were handled by listwise deletion. Statistical analyses were conducted at a 2-tailed α level of 0.05. The data were analyzed using Stata version 17.

Results

Among 5,429 patients treated with EVT, 1,224 had a complete angiographic reperfusion. One hundred thirty-one patients were further excluded because the mRS status at 90 days was unknown ($n = 130$) and IVT status was unknown ($n = 1$). The final study population consisted of

1,093 patients, 651 of whom were treated with IVT and 442 without IVT before EVT (Figs 1 and S1). In the overall cohort, the IVT+EVT group had a younger mean age (71 vs 74 years, $p < 0.001$), had less hypertension (58.1% vs 67.4%, $p = 0.002$), hypercholesterolemia (28.1% vs 36%, $p = 0.006$), diabetes (15.6% vs 21.1%, $p = 0.019$), prior stroke (13.2% vs 23.1%, $p < 0.001$), ischemic heart disease (14.8% vs 22.7%, $p = 0.001$), and prestroke mRS 0–2 (94.6% vs 91.3%, $p = 0.041$), was less likely to receive anticoagulation before AIS (7.7% vs 41.7%, $p < 0.001$), and was less likely to have a cardioembolic etiology (47.3% vs 64.3%, $p < 0.001$) compared with the EVT alone group (Table 1). We did not find significant imbalances regarding the site of vascular occlusion between the two groups in either the whole cohort ($p = 0.089$) or the matched cohort ($p = 0.326$; see Table 1). In terms of procedural characteristics, the IVT+EVT group was more likely to be first admitted to a primary stroke center (52.6% vs 38.8%, $p < 0.001$) and

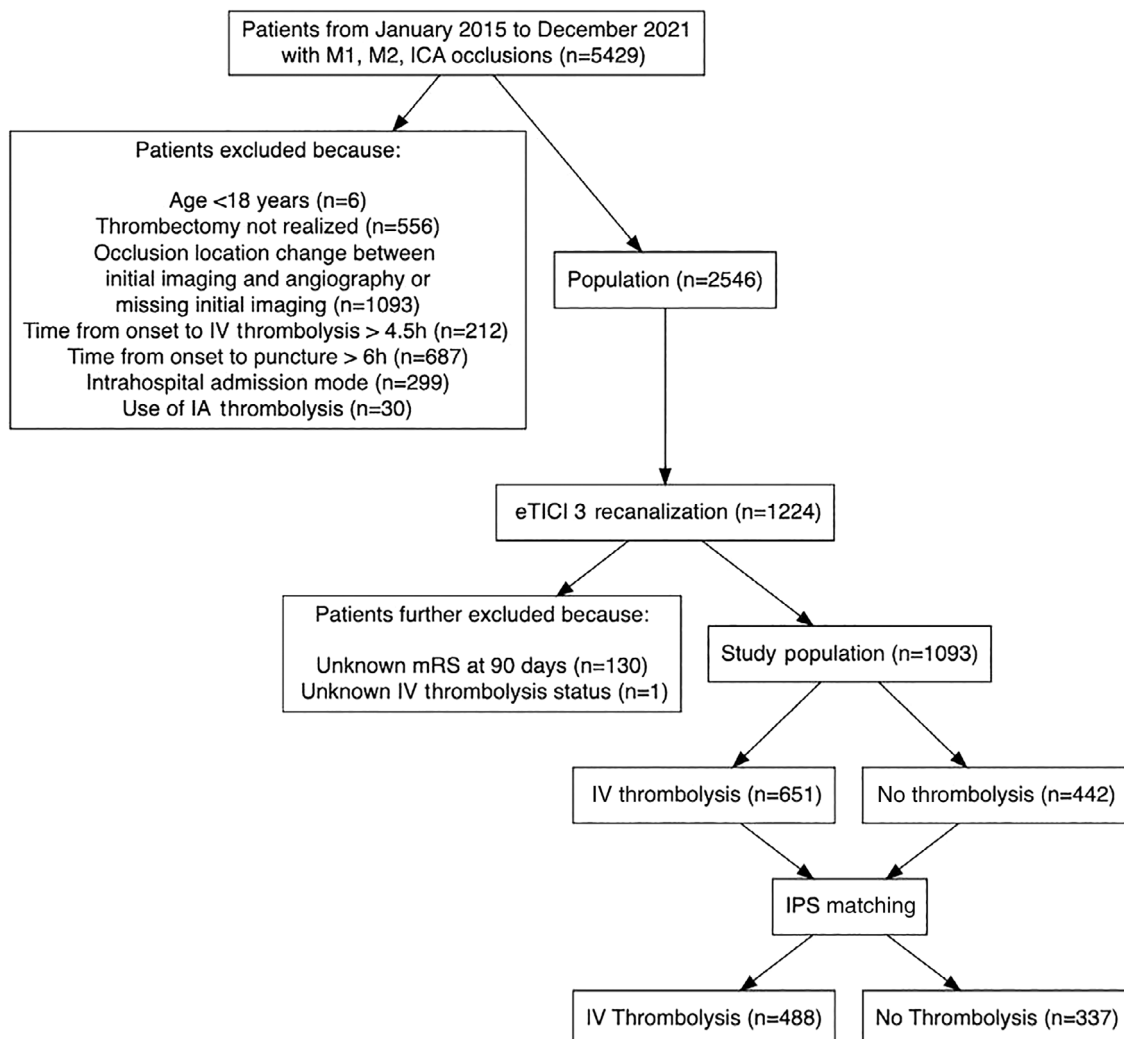


FIGURE 1: Study flowchart. eTICI = expanded Thrombolysis in Cerebral Infarction; IA = intra-arterial; ICA = internal carotid artery; IV = intravenous; mRS = modified Rankin Scale; IPS = Inverse propensity score.

TABLE 1. Demographic and Procedural Characteristics for the Full and Inverse Propensity Matched Cohort^a

Characteristic	Full Cohort			Matched Cohort		
	IVT+EVT, n = 651	EVT Alone, n = 442	<i>p</i>	IVT+EVT, n = 488	EVT Alone, n = 337	IPS-Weighted <i>p</i>
Age, mean (SD)	71 (14)	74 (13)	<0.001	71.3 (20)	71.7 (16)	0.749
Female, n (%)	325 (49.9)	227 (51.4)	0.642	236 (48.4)	172 (51.0)	0.946
Hypertension, n (%)	373 (58.1)	295 (67.4)	0.002	280 (57.4)	227 (67.4)	0.801
Hypercholesterolemia, n (%)	179 (28.1)	155 (36.0)	0.006	137 (28.1)	117 (34.7)	0.748
Smoking, n (%)	92 (14.9)	66 (15.8)	0.700	74 (15.2)	55 (16.3)	0.877
Diabetes, n (%)	100 (15.6)	92 (21.1)	0.019	77 (15.8)	64 (19.0)	0.178
Prior stroke, n (%)	85 (13.2)	100 (23.1)	<0.001	69 (14.1)	75 (22.3)	0.762
Ischemic heart disease, n (%)	95 (14.8)	99 (22.7)	0.001	70 (14.3)	68 (20.2)	0.920
Pre-stroke mRS 0–2, n (%)	591 (94.6)	390 (91.3)	0.041	461 (94.5)	307 (91.1)	0.861
Antiplatelet therapy, n (%)	161 (25.3)	103 (23.6)	0.528	124 (25.4)	82 (24.3)	0.883
Anticoagulation, n (%)	49 (7.7)	181 (41.7)	<0.001	32 (6.6)	136 (40.4)	0.805
SBP, mean (SD)	146 (26)	148 (26)	0.253	146 (41)	148 (30)	0.390
DSP, mean (SD)	81 (17)	82 (16)	0.232	80 (22)	82 (15)	0.099
Blood glucose, mean (SD)	7 (3)	7 (3)	0.922	7 (3)	7 (3)	0.743
NIHSS, median (IQR)	16 (10)	17 (9)	0.176	17 (10)	17 (9)	0.733
ASPECTS, median (IQR)	8 (2)	8 (3)	0.554	8 (2)	8 (4)	0.734
Etiology, n (%)						
Atherosclerosis	68 (10.8)	22 (5.1)		52 (10.7)	18 (5.3)	
Cardioembolic	299 (47.3)	277 (64.3)		237 (48.6)	217 (64.4)	
Other	265 (41.9)	132 (30.6)	<0.001	199 (40.8)	102 (30.3)	0.612
Admission mode, N (%)						
Mothership	304 (47.4)	265 (61.2)		242 (49.6)	218 (64.7)	
Drip and ship	338 (52.6)	168 (38.8)	<0.001	246 (50.4)	119 (35.3)	0.842
Occlusion location						
M1	481 (73.9)	302 (68.3)		362 (74.2)	229 (68.0)	
M2	84 (12.9)	62 (14.0)		66 (13.5)	46 (13.6)	
Intracranial ICA	86 (13.2)	78 (17.6)	0.089	60 (12.3)	62 (18.4)	0.326
General anesthesia, n (%)	119 (18.4)	122 (27.9)	<0.001	81 (16.6)	90 (26.7)	0.878
First-line EVT strategy, n (%)						
Stentriever	43 (6.7)	26 (6.0)		34 (7.0)	21 (6.3)	
Aspiration	289 (44.9)	193 (44.3)		224 (46.4)	150 (45.2)	
Stentriever and aspiration	311 (48.4)	217 (49.8)	0.842	225 (46.6)	161 (48.5)	0.822
Time from symptom onset to puncture, median (IQR)	232 (105)	220 (100)	0.010	218 (100)	225 (93)	0.886

^aInverse propensity matched cohort matched for age, hypertension, hypercholesterolemia, smoking, ischemic heart disease, anticoagulation, etiology, prior stroke, initial mRS, admission mode, baseline NIHSS, baseline ASPECTS, general anesthesia, and time from symptom onset to puncture. Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; DBP = diastolic blood pressure; EVT = endovascular therapy; ICA = internal carotid artery; IPS = inverse propensity score; IQR = interquartile range; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SBP = systolic blood pressure; SD = standard deviation. Unit of SBP and DSP is mmHg/Unit of blood glucose is mmol/L/Unit of time is minutes

more likely to be treated under general anesthesia (18.4% vs 27.9%, $p < 0.001$) but had a longer median time from symptom onset to puncture (232 vs 220 minutes, $p = 0.010$). The remaining demographic and procedural characteristics were comparable between both groups. For differentiating eTICI 3 from eTICI 2c reperfusion grades, multirater kappa was 0.44.

Efficacy Outcomes in the Matched Cohort

There was a significant shift toward a lower degree of functional disability on the mRS score at 90 days (adjusted odds ratio [aOR] = 1.41, 95% CI = 1.04–1.91, $p = 0.023$) favoring the IVT+EVT group compared to the EVT alone group (Fig 2). The ordinal logistic regression model for 1-point improvement on the mRS at 90 days and OR estimates for all included variables is displayed in Table S1. Rates of favorable outcome at 90 days were also significantly higher in the IVT+EVT group compared with the EVT alone group (aOR = 1.49, 95% CI = 1.02–2.20, $p = 0.041$; Table 2). However, favorable outcome at 90 days was not associated with the (aOR = 0.99, 95% CI = 0.99–1.00, $p = 0.992$). We did

not find significant associations for excellent outcome at 90 days (aOR = 1.27, 95% CI = 0.86–1.87, $p = 0.23$) and early neurological improvement at 24 hours (aOR = 1.33, 95% CI = 0.93–1.90, $p = 0.12$). In the subgroup of patients treated with IVT prior to EVT, the time from symptom onset to IVT administration had no significant effect on mRS 0–2 at 90 days (aOR = 1.00, 95% CI = 0.99–1.01, $p = 0.383$).

Safety Outcomes in the Matched Cohort

The IVT+EVT group had lower odds of mortality at 90 days compared with the EVT alone group (10.5% vs 19.3%, aOR = 0.53, 95% CI = 0.31–0.92, $p = 0.022$). However, we found similar rates of parenchymal hematoma (9.8% vs 5.7%, aOR = 1.44, 95% CI = 0.70–2.94, $p = 0.319$) and sICH (6.0% vs 4.3%, aOR = 1.16, 95% CI = 0.53–2.54, $p = 0.709$; see Table 2). Of note, in the subgroup of patients treated with IVT prior to EVT, the time from symptom onset to IVT administration had no significant effect on the occurrence of PH (aOR = 0.99, 95% CI = 0.98–1.00, $p = 0.631$) and sICH (aOR = 0.99, 95% CI = 0.97–1.00, $p = 0.406$).

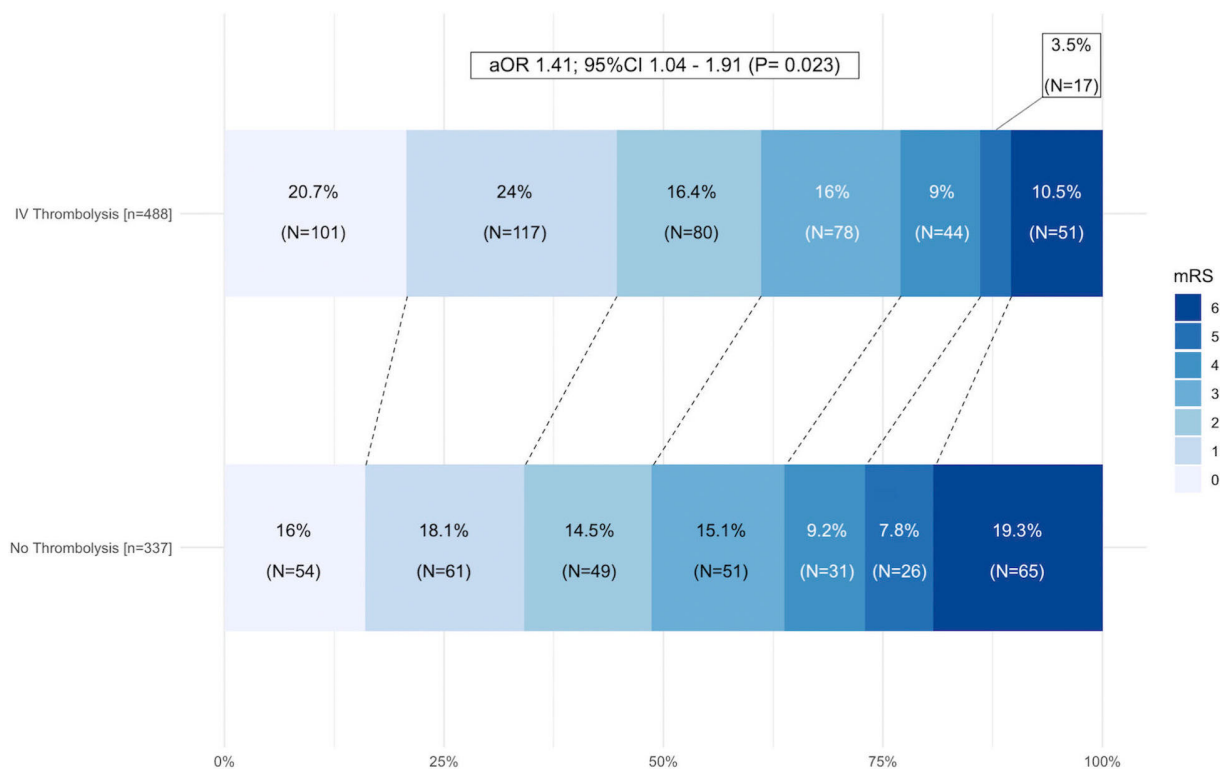


FIGURE 2: Shift analysis of the modified Rankin Scale (mRS) at 90 days in the matched cohort. Shown are scores on the mRS for patients with intravenous thrombolysis + endovascular therapy (EVT) and for those with EVT alone. The adjusted odds ratio (aOR) was calculated from an inverse propensity score-adjusted proportional odds model. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help, but able to walk unassisted; 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. CI = confidence interval; IV = intravenous. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 2. Efficacy and Safety Outcomes for the Matched Cohort

Outcome	IVT+EVT, n = 488		Univariable			Multivariable ^a		
	EVT Alone n = 337		Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
Early neurological improvement, n (%)	306 (62.7)	203 (60.2)	1.28	0.91–1.79	0.157	1.33	0.93–1.90	0.120
mRS 0–2 at 90 days, n (%)	298 (61.1)	164 (48.7)	1.35	0.96–1.89	0.081	1.49	1.02–2.20	0.041
mRS 0–1 at 90 days, n (%)	218 (44.7)	115 (34.1)	1.19	0.84–1.68	0.334	1.27	0.86–1.87	0.230
Number of passes ≥ 2, n (%)	271 (80.2)	225 (79.8)	1.09	0.68–1.74	0.716	1.09	0.67–1.77	0.720
Mortality, n (%)	51 (10.5)	65 (19.3)	0.61	0.38–0.98	0.041	0.53	0.31–0.92	0.022
PH hemorrhage, n (%)	38 (9.8)	16 (5.7)	1.40	0.70–2.80	0.337	1.44	0.70–2.94	0.319
Symptomatic intracranial hemorrhage n (%)	25 (6.0)	13 (4.3)	1.15	0.53–2.49	0.720	1.16	0.53–2.54	0.709
Time from puncture to reperfusion, median (IQR)	30 (21)	31 (22)	Coef. –1.51	–5.88 to 2.86	0.497	Coef. –1.42	–5.77 to 2.91	0.518

^aAdjusted for age/National Institutes of Health Stroke Scale/Alberta Stroke Program Early CT Score/time from onset to puncture with an inverse propensity score-weighted linear logistic regression model.
CI = confidence interval; Coef. = coefficient; EVT = endovascular therapy; IQR = interquartile range; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; PH = parenchymal hemorrhage.

Subgroup Analysis

As shown in Figure 3, IVT use before EVT was associated with an increased rate of favorable outcome at 90 days in patients with baseline NIHSS >20 and in patients treated with >2 passes.

Regarding mortality at 90 days, IVT use before EVT was associated with decreased rates of mortality in patients with >2 passes (Fig S2).

Discussion

In a large multicenter cohort of AIS patients with anterior circulation LVO and complete angiographic reperfusion (eTICI 3) at the end of EVT, we found that patients treated with IVT before EVT had higher rates of functional independence at 90 days. In addition, the IVT +EVT group had lower mortality at 90 days, with similar sICH and PH rates compared with the EVT alone group.

Effective tissue reperfusion is the optimal goal of AIS treatment and seems to be a greater predictor of improved clinical outcome than arterial recanalization.^{16,17} In the present study, included patients had a persistent proximal occlusion on the first angiographic run before EVT, consistent with the baseline pre-IVT imaging. Therefore, our hypothesis is that the improved functional outcome observed in this study may be explained by tissue reperfusion (in addition to arterial

recanalization). Applied to acute myocardial infarction, the no-reflow phenomenon (ie, absence of tissue reperfusion despite successful arterial recanalization) is associated with microvascular obstruction on cardiac MRI, seems frequent with an incidence >50%, and is also associated with increased adverse in-hospital and long-term outcomes.^{25,26} In the AIS setting, the concept of microvascular obstruction involving the no-reflow phenomenon is still debated.²⁷ In a recent study by Ng et al, the no-reflow was associated with tissue hypoperfusion despite successful recanalization, blood–brain barrier damage, hemorrhagic transformation, and infarct growth, resulting in poor outcome.²⁸ More specifically, in patients with near-to-perfect angiographic reperfusion (ie, eTICI 2c–3) after EVT and with 24-hour follow-up CT or MRI perfusion imaging, the rate of no-reflow reached 20.5% and 31.6% in eTICI 2c and eTICI 3 patients, respectively.²⁸ In this context, new tools are needed to assess cerebral perfusion in the acute setting after EVT. The assessment of brain perfusion, using cone-beam CT perfusion immediately after angiographic reperfusion in the catheterization laboratory, could be a promising approach to tailor the patient's management after successful EVT.^{29,30} Because arterial recanalization by EVT has now been mastered by most teams worldwide, efforts should be directed toward the evaluation and therapeutic targeting of microvascular

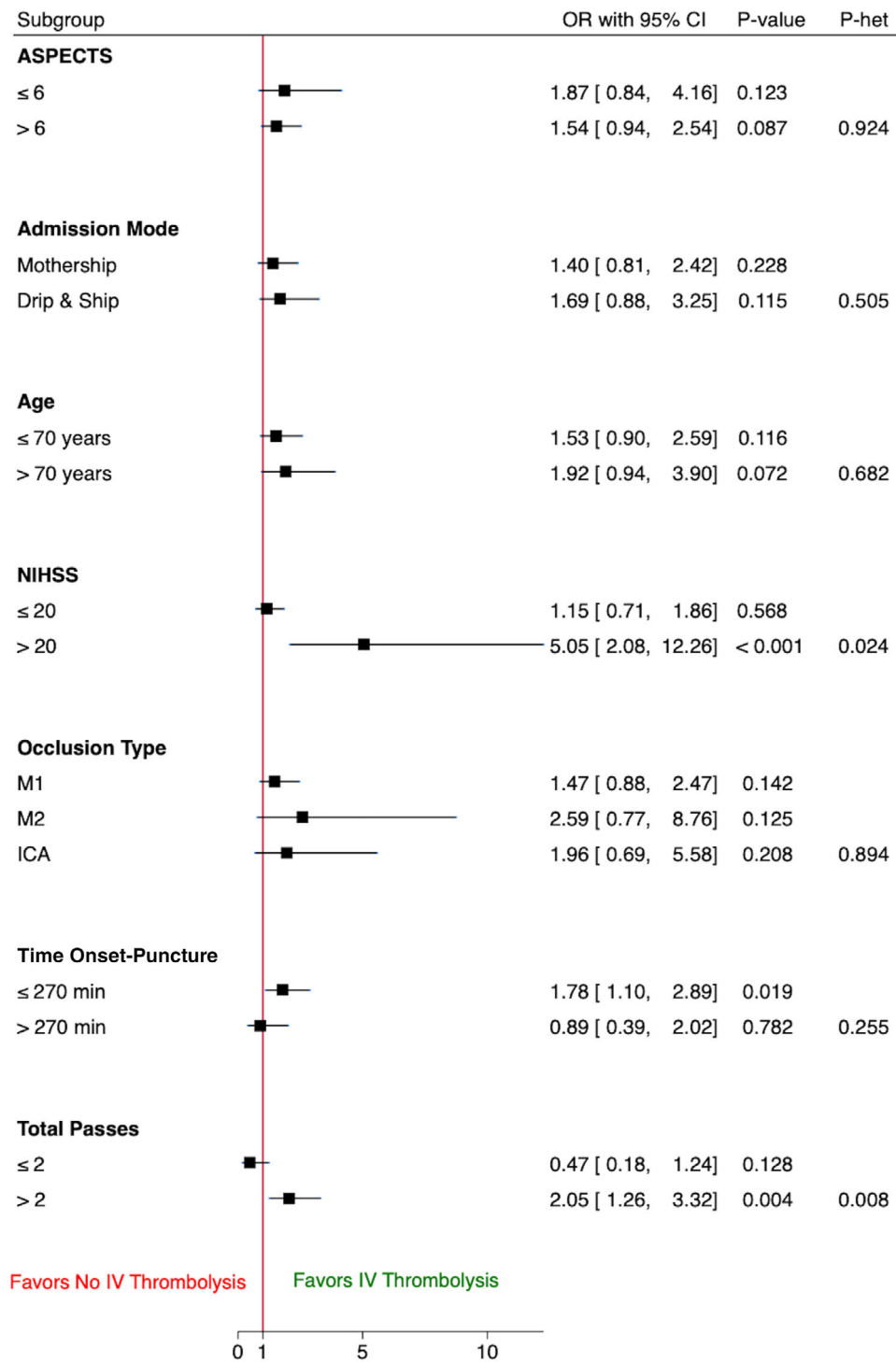


FIGURE 3: Treatment effect size of intravenous thrombolysis on favorable outcome at 90 days across different subgroups in the matched cohort. ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; ICA = internal carotid artery; IV = intravenous; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio. [Color figure can be viewed at www.annalsofneurology.org]

thrombolysis after and despite successful angiographic reperfusion. In this context, the MR-Reperfusion study (MRI Biomarkers of Effective Tissue Reperfusion After Thrombectomy of an Acute Proximal Occlusion of the Anterior Circulation, NCT04952077) could provide new insights, with a

longitudinal assessment of tissue perfusion at baseline, immediately after EVT, and 24 hours, 7 days, and 90 days after complete angiographic reperfusion (ie, eTICI 3).

IVT use before EVT was associated with an increased rate of favorable outcome at 90 days in patients

with baseline NIHSS >20 and in patients who underwent >2 passes during EVT. Several preclinical as well as clinical studies performed by our team and others demonstrated that the size of the core, neutrophil extracellular trap covering the clot and making it more difficult to retrieve, and the endothelial damage caused by repetitive devices passes all contribute to the thromboinflammatory cascade initiated in the microcirculation downstream of LVO.^{31–38} We speculate that these effects could be mitigated by IVT use prior to EVT, in the situation of complete angiographic reperfusion by EVT. That said, these results are only exploratory, as the propensity score matched analysis concerned the use of IVT prior to EVT and not baseline NIHSS or the number of passes. Several confounders (such as age, arterial occlusion site, and vascular risks factors) may therefore also explain these findings, and future studies are warranted to confirm these results in these specific subgroups.

Downstream microvascular obstruction may be treated with intravenous and/or intra-arterial medications (ie, antiplatelets, thrombolysis) after successful EVT.^{15,31} The recent positive results of the phase 2b CHOICE randomized trial, in which intra-arterial alteplase after successful EVT led to increased rates of excellent outcome at 90 days, should be confirmed in further trials.^{15,39} As such, different therapeutic targets are currently being investigated in the IA-SUCCESS (Intra-Arterial Thrombolysis after Successful Angiographic Reperfusion in Acute Large Vessel Occlusion Stroke of the Anterior Circulation) multicenter, randomized clinical trial and CHOICE2 (Chemical Optimization of Cerebral Embolectomy 2, NCT05797792). The REPERFUSE (Reperfusion with P2Y12 Inhibitors in Addition to Mechanical Thrombectomy for Perfusion Imaging Selected Acute Stroke Patients, NCT04667078) trial will evaluate the safety and efficacy of an intravenous P2Y12 inhibitor (cangrelor) in addition to EVT on functional outcome at 90 days. The GREEN (Glenzocimab for Reperfusion in the Setting of Endovascular Therapy for Brain Infarction, NCT05559398) trial is evaluating the efficacy of glenzocimab (an antiplatelet agent targeting the glycoprotein VI receptor) in addition to EVT versus placebo on functional outcome at 90 days. Regarding anti-glycoprotein IIb/IIIa, the recent RESCUE-BT trial did not show improved functional outcome at 90 days of tirofiban versus placebo.⁴⁰ Finally, the MOST (Multi-Arm Optimization of Stroke Thrombolysis, NCT03735979) study is a multicenter, multiarm, adaptive, randomized controlled trial evaluating whether the use of argatroban (a direct thrombin inhibitor) for 12 hours or eptifibatid (anti-glycoprotein IIb/IIIa) for 2 hours in AIS patients treated with IVT with or without EVT will result in improved functional outcome

at 90 days as compared with placebo.⁴¹ As suggested above, imaging outcomes will be mandatory to comprehensively understand the effect of these treatments on downstream microvascular thrombosis. As such, patients included in the REPERFUSE, GREEN or IA-SUCCESS studies, for instance, will also participate in the MR-REPERFUSION study, to provide new insights into the effects of these treatments on post-EVT perfusion imaging.

This study presents several strengths, including its multicenter design (21 comprehensive stroke centers) and a large sample of patients. However, several limitations must be acknowledged. First, despite the prospective design of the ETIS registry, the present study is retrospective and observational, thus potentially leading to confounding bias in the analysis. To address this limitation, we performed a propensity score-matched analysis, but this method cannot completely adjust for other unknown confounders. Specifically, EVT alone patients were either directly referred to a comprehensive stroke center or transferred from a primary stroke center. For these patients, the lack of IVT prior to EVT could have been deleterious, given the time for transfer to the comprehensive stroke center, notably despite the propensity score-matched design. In addition, our results mainly apply to M1 occlusions (71%). Therefore, other sites of LVO (ie, internal carotid artery or M2) may be associated with different post-EVT hypoperfusion volume. Second, systematic perfusion imaging was not performed after successful angiographic reperfusion by EVT. Therefore, this study cannot fully demonstrate that the positive effect played by IVT is driven by improved microvascular reperfusion compared to EVT. Third, our results mainly apply to alteplase use prior to EVT, as only 5.6% of the included patients were treated with tenecteplase before EVT. Finally, there was no central adjudication of outcomes. However, clinical outcomes were assessed by certified vascular neurologists or research nurses, and radiological outcomes were assessed by certified neuroradiologists at each center. That said, neurologists and research nurses who evaluated the clinical outcomes at 90 days were not strictly blinded to the initial treatment, as they could have access to the patient's clinical file.

Conclusions

In the setting of a complete angiographic reperfusion (eTICI 3), patients treated with IVT before EVT had better functional outcomes and lower rates of mortality. Randomized trials are needed to assess the safety and efficacy of treatments targeting downstream microvascular thrombosis, especially in the context of a successful angiographic reperfusion.

Author Contributions

B.G. contributed to the conception and design of the study. B.M., S.F., M.M., B.L., G.M., I.S., S.R., A.V., C.C., B.G., and J.-M.O. contributed to the acquisition and analysis of data. B.M., S.F., M.M., B.L., G.M., I.S., S.R., A.V., C.C., B.G., and J.-M.O. contributed to drafting the text and preparing the figures. A.C. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

J.-M.O. declares consulting activities with Abbvie, Acticor and Bioxodes; and speaking fees from BMS and Boehringer Ingelheim. S.F. is the author of a patent (US20200085454A1). B.M. declares a grant from the French Health Ministry and is the primary investigator of the DETERMINE trial. B.G. has received grants from the French Ministry of Health, is the primary investigator of the TITAN, DIRECT ANGIO, and IA-SUCCESS trials, and has received consulting fees from Air Liquide, MIVI, Medtronic, Microvention, and Penumbra. M.M. declares consulting fees from Boehringer Ingelheim, Air Liquide, Acticor Biotech, and Amgen. S.R. declares contracts from Boehringer Ingelheim France, Bristol Myers Squibb, and Pfizer.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX

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