Thrombectomy with or without Intravenous Thrombolytics in Basilar Artery Occlusion

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Objective: Two randomized trials demonstrated the benefit of endovascular therapy (EVT) in patients suffering from a stroke due to a basilar artery occlusion (BAO). However, intravenous thrombolytic (IVT) use before EVT was low in these trials, questioning the added value of this treatment in this setting. We sought to investigate the efficacy and safety of EVT alone compared to IVT + EVT in stroke patients with a BAO.

Methods: We analyzed data from the Endovascular Treatment in Ischemic Stroke registry, a prospective, observational, multicenter study of acute ischemic stroke patients treated with EVT in 21 centers in France between 1 January 2015 and 31 December 2021. We included patients with BAO and/or intracranial vertebral artery occlusion and compared patients treated with EVT alone versus IVT + EVT after propensity score (PS) matching. Variables selected for the PS were pre-stroke mRS, dyslipidemia, diabetes, anticoagulation, admission mode, baseline NIHSS and ASPECTS, type of anesthesia, and time from symptom onset to puncture. Efficacy outcomes were good functional outcome (modified Rankin Scale [mRS] 0-3) and functional independence (mRS 0–2) at 90 days. Safety outcomes were symptomatic intracranial hemorrhages and all-cause mortality at 90 days.

Results: Among 385 patients, 243 (134 EVT alone and 109 IVT + EVT) were included after PS matching. There was no difference between EVT alone and IVT + EVT regarding good functional outcome (adjusted odd ratio [aOR] labeling = 1.27, 95% confidence interval [CI], 0.68–2.37, $p = 0.45$) and functional independence (aOR = 1.50, 95% CI, 0.79–2.85, $p = 0.21$). Symptomatic intracranial hemorrhage and all-cause mortality were also similar between the two groups (aOR = 0.42, 95% CI, 0.10–1.79, $p = 0.24$ and aOR = 0.56, 95% CI, 0.29–1.10, $p = 0.09$, respectively).

Interpretation: In this PS matching analysis, EVT alone seemed to lead to similar neurological recovery than IVT + EVT, with comparable safety profile. However, given our sample size and the observational nature of this study, further studies are needed to confirm these findings.

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Introduction

Recent randomized clinical trials have clarified the management of acute ischemic stroke (AIS) patients due to basilar artery occlusions (BAO), showing a superiority in terms of improved functional outcomes with endovascular therapy (EVT) and best medical treatment (including intravenous thrombolytics [IVT]) compared to best medical treatment alone, within 24 h after symptom onset.[1,2] Interestingly, the Chinese ATTENTION (*Endovascular Treatment for Acute Basilar-Artery Occlusion*), BAOCHE (*Basilar Artery Occlusion Chinese Endovascular*), and BEST (*Basilar Artery Occlusion Endovascular Intervention versus Standard Medical* Treatment) trials significantly differed in their design and results with the European BASICS (*Basilar Artery International Cooperation Study*) trial.[1–4] Notably, IVT use prior to EVT was low in the EVT arm of the ATTENTION, BAOCHE and BEST trials (31%, 14% and 27%, respectively) as compared to the BASICS trial (78.6%),[1–3] because (1) payment was required before IVT initiation, and (2) time from symptom onset to randomization often exceeded 4.5 h.[4] However, rates of good functional outcomes (modified Rankin Scale [mRS] 0-3 at 90 days) and functional independence (mRS 0–2 at 90 days) in the EVT arm, remained numerically similar between the ATTENTION and BAOCHE trials and the BASICS trial.[1–3] In addition, rates of successful reperfusion (defined by a modified Treatment in Cerebral Ischemia [mTICI] 2b-3) were higher in the ATTENTION (93%) and BAOCHE (88%) trials compared to the BASICS trial (72%),[2,3,5] altogether questioning the added value of IVT in this setting. In the setting of anterior large vessel occlusions (LVO), the effect of IVT before EVT has been recently evaluated in several non-inferiority randomized controlled trials, with conflicting results, but with overall no significant increase in the risk of ICH by the use of thrombolytics before EVT.[6–11] Importantly, the risk of ICH was also not increased in seminal anterior circulation EVT trials compared to the medical management alone. This result differs with the BASICS, BAOCHE, and ATTENTION trials, in which the risk of ICH was significantly increased in the IVT + EVT groups compared to medical management alone. It is therefore possible that the effect played by thrombolytics in the posterior circulation might differ from that of the anterior circulation and explain the increased risk of ICH, especially when EVT is performed. With this as a background, we sought to compare the effectiveness and safety of EVT alone versus IVT prior to EVT (IVT + EVT), using data from a national multicenter prospective registry. Our primary hypothesis was that IVT + EVT would not result in significantly increased effectiveness in terms of good functional outcome or reperfusion rates compared to EVT alone, but that the latter would be associated with lower rates of hemorrhagic complications compared to IVT + EVT.

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 in 21 comprehensive stroke centers in France. Data of the ETIS registry were collected and analyzed according to the recommandations of the "*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé*". This study was approved by the ethical committee (ID RCB 2017-A03457-46). Written informed consent was obtained from all patients or their legal representatives. Details regarding data collection and materials have been previously published.[12] As the present study is observational, the adherence to the STROBE criteria was enforced.

For the present study, we included adult patients (≥18 years old) with a posterior large vessel occlusion (basilar artery and/or intracranial segment of the vertebral artery) treated by EVT between 1 January 2015 and 31 December 2021. Patients were also included if a complete recanalization was seen on the first angiographic run and no additional therapeutic maneuver was performed. Patients with isolated posterior cerebral artery occlusion, posterior LVO 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 posterior circulation Alberta Stroke Program Early CT score (PC-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 EVT strategy included the use of last-generation stent retrievers and/or thrombo-aspiration. Rescue treatments in case of

EVT failure (lack or reperfusion despite several intracranial passages and/or re-occlusion) included intracranial balloon angioplasty, stent deployment with or without intravenous antiplatelet therapy (aspirin, anti-GP IIbIIIa or intra-arterial alteplase), on a case-by-case basis according to the operators' decision and local protocols. Successful and complete reperfusion were defined as a mTICI score of 2b-3 and 3, respectively. Final mTICI score were assessed by one neuroradiologist for each center (>10 years of experience), prospectively, blinded to the results of clinical outcome. CT scan or brain MRI were performed systematically 24 h after EVT and also analyzed by one neuroradiologist (>10 years of experience) of each center blinded to the procedure and clinical outcome. Functional outcome was assessed by certified neurologists or research nurses with the mRS at 90 days, during face-to-face interviews or phone calls with the patient or their relatives.

Clinical and Radiological Outcomes

Clinical outcomes consisted of good functional outcome, defined as a mRS between 0 and 3 at 90 days;[1,2] functional independence, defined as a mRS between 0 and 2 at 90 days; the distribution of scores on the mRS at 90 days (ordinal scale), and the NIHSS at 24 h. Safety outcomes included parenchymal hemorrhages (PH), symptomatic intracranial hemorrhage, defined as any intracranial hemorrhages on the 24-h brain CT associated with an increase of four points or more on the NIHSS within 24 h attributable to the ICH,[5] all-cause mortality at 90 days, and procedural complications (dissection, arterial perforation, embolization to a new territory).

Statistical Analysis

Quantitative variables are expressed as mean (standard deviation [SD]) for normally distributed parameters or median (interquartile range [IQR]) otherwise. Categorical variables are expressed as numbers (percentages). Patients were divided between two groups according to IVT use prior to EVT. Baseline characteristics were compared between these two groups using the Student's *t*-test for Gaussian continuous variables, Mann–Whitney U-test for non-Gaussian continuous variables, or χ^2 test (or Fisher's exact test when the expected cell frequency was <5) for categorical variables, as appropriate.

Missing data were imputed under the missing at random assumption by using a regression-switching approach (chained equation with $m = 10$ imputations) using all the baseline characteristics with a predictive mean matching method for continuous variables and a multinomial or binary logistic regression model for categorical variables. To reduce the effects of potential confounding factors between the two groups, we used propensity-score methods. The propensity score was used to assemble well-balanced groups (propensity score-matched cohort) and a generalized linear mixed model was used to take into account the matched design. The effect of the therapeutic approach was estimated using the inverse probability of treatment weighting (IPTWT) propensity score method (using inverse propensity score as weight in simple logistic regression model). The propensity score for each patient was defined as the probability of being on the treatment (ie, IVT) given the patient's pre-stroke modified Rankin scale, hypercholesterolemia, diabetes, baseline anticoagulation, admission mode, baseline NIHSS, baseline ASPECTS, type of anesthesia, rescue therapy, and the time from symptom onset to puncture. Subsequently, nearest-neighbor matching was performed on the derived propensity score with replacement setting a caliper of 0.25 SD of the logit for propensity score. Sensitivity analyses were further performed using inverse propensity score matching in the subgroup of patients with BAO and according to the admission mode (drip and ship versus mother ship) and the etiology (intracranial atherosclerosis versus no intracranial atherosclerosis). Estimates obtained in the different imputed data sets were combined using the Rubin rules. Effects are presented as odds ratios (OR) with 95% confidence intervals (CI) and were calculated with univariate and multivariate logistic regression models adjusted for age, baseline NIHSS, PC-ASPECTS, and the time from symptom onset to puncture. Statistical analyses were conducted at a 2-tailed α level of 0.05. The data were analyzed using STATA ver. 17.

Results

Between 1 January 2015 and 31 December 2021, 486 patients were included in the ETIS registry with a basilar artery or an intracranial vertebral artery occlusion (Figure). Among these patients, 92 (18.9%) were excluded because IVT status was unknown ($n = 3$) or EVT was not performed, for the following reasons: unfavorable benefit/risk ratio after completion of the first angiographic run ($n = 10$), failure to catheterize or advance devices ($n = 20$), unrecorded reasons ($n = 31$), unrecorded location of arterial occlusion ($n = 28$). Altogether, 394 patients for whom EVT was performed or with complete recanalization seen in the first angiographic run were included, 151 patients received IVT prior to EVT (38.3%), 243 patients without IVT (61.6%), Figure . Reasons for not administering IVT are given in Table S1. Table 1 shows baseline characteristics and stroke characteristics according to the two study groups (IVT versus no IVT) before and after multiple imputation and propensity score matching. Before matching, several

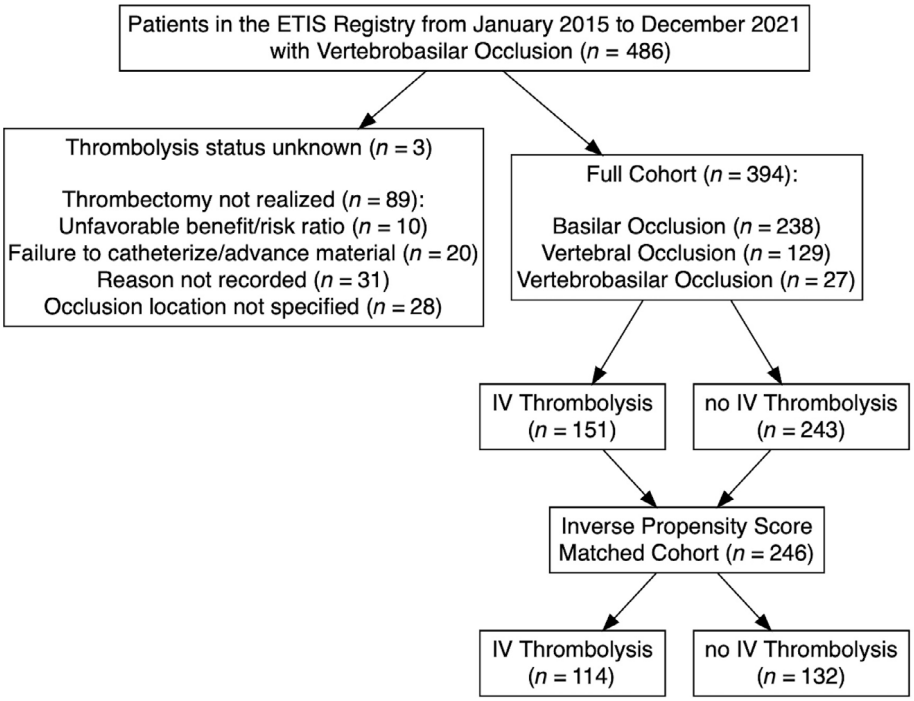

FIGURE: Study Flow Chart

meaningful differences were found: patients treated with IVT were less likely to have hypertension (51.7% vs 65.8%, $p = 0.006$) and a history of stroke (10.3% vs 22.9%, $p = 0.002$), were less often treated with anticoagulation (8.2% vs 17.2%, $p = 0.012$), had a lower median NIHSS (12 vs 17, $p = 0.001$), had a lower median PC-ASPECTS (8, IQR = 3 versus 8, IQR = 4, $p = 0.013$), were more often referred from a primary stroke center (48% versus 38.4%, $p = 0.001$), were less likely to receive general anesthesia (59.1% vs 69.4%, $p = 0.036$), and to rescue therapy (6.8% vs 20.9%, $p = 0.003$) and had shorter median time from onset to puncture (270 min vs 318 min, $p = 0.007$). A total of 246 patients were included in the propensity score analysis (Table 1), of whom 114 (46.3%) received IVT prior to EVT. Between-group differences in baseline characteristics were reduced after propensity score matching (Table 1).

Effectiveness and Safety of EVT Alone Versus IVT + EVT in the Matched Cohort

In the matched cohort, 65 patients (59.6%) and 70 patients (55.1%) reached good functional outcome (mRS 0–3) at 90 days in the IVT + EVT and EVT alone groups, respectively. IVT + EVT was not associated with good functional outcome at 90 days (aOR = 1.23; 95% CI, 0.67–2.25, $p = 0.51$), Table 2. Similarly, 53 patients (48.6%) and 55 patients (43.3%) reached functional independence (mRS 0–2) at 90 days in the IVT + EVT and EVT alone groups, respectively, and IVT + EVT was not associated with functional independence at 90 days (aOR = 1.28; 95% CI, 0.73–2.24, p = 0.39). The adjusted OR for a 1-point improvement on the mRS scale at 90 days was 0.72 (95% CI, 0.44–1.18), $p = 0.19$. A successful reperfusion (mTICI 2b-3) was achieved in 105 patients (93.8%) in the IVT + EVT group and 118 patients (94.4%) in the EVT alone group and did not significantly differ between the two groups (aOR = 1.00; 95% CI, 0.27–3.73, $p = 0.99$).

Regarding safety outcomes, the occurrence of a parenchymal hemorrhage (2 patients (2.1%) in the IVT + EVT group and 3 patients (2.8%) in the EVT alone group) and symptomatic ICH (2 patients (2.0%) in the IVT + EVT group and 6 patients (5.1%) in the EVT alone group) did not differ between the two groups (aOR = 0.85; 95% CI, 0.18–4.15, $p = 0.84$ and aOR = 0.40; 95% CI, 0.09–1.77, $p = 0.22$, respectively). All-cause mortality at 90 days also did not differ between IVT + EVT and EVT alone (aOR = 0.63; 95% CI, 0.33–1.23, $p = 0.17$).

In the subgroup of patients with isolated BAO (Table S2), efficacy and safety outcomes did not differ between the two groups. In the subgroup of patients transferred from a primary stroke center (Table S3), there was a decreased mortality in the group of patients treated with IVT prior to EVT (aOR = 0.32, 95% CI, 0.11–0.94, $p = 0.038$), but other efficacy and safety outcomes did not differ between the two groups.

The effect of IVT prior to EVT according to the etiology (ie, intracranial atherosclerosis versus no intracranial

TABLE 1. Demographics for the Full Cohort and Inverse Propensity Matched Cohort

	Full Cohort ($N = 394$)				Matched Cohort* ($N = 246$)		
	IVT + EVT ($N = 151$)	EVT alone ($N = 243$)	*p*-value	Missing	IVT + EVT ($N = 114$)	EVT alone ($N = 132$)	IPS weighted *p*-value
Age, mean (SD)	66 (14)	66 (15)	0.984	0 (0)	66.7 (16.0)	66.8 (15.0)	0.989
Female, *N* (%)	46 (30.5)	86 (35.4)	0.314	0 (0)	37 (32.7)	48 (36.1)	0.722
Hypertension, *N* (%)	76 (51.7)	152 (65.8)	0.006	16 (4)	63 (55)	84 (63.6)	0.213
Hypercholesterolemia, *N* (%)	40 (27.8)	79 (35.0)	0.150	24 (6)	44 (38.5)	45 (34.1)	0.522
Smoking, *N* (%)	41 (29.1)	63 (29.0)	0.993	36 (9.1)	30 (26.3)	35 (26.5)	0.998
Diabetes, *N* (%)	39 (26.5)	43 (18.9)	0.079	19 (4.8)	25 (21.9)	31 (23.4)	0.783
Prior Stroke, *N* (%)	15 (10.3)	52 (22.9)	0.002	22 (5.5)	19 (16.6)	29 (21.9)	0.344
Coronaropathy, *N* (%)	18 (12.4)	36 (16.0)	0.340	24 (6)	16 (14)	18 (13.6)	0.956
Pre-Stroke mRS 0–2, *N* (%)	140 (96.6)	218 (95.2)	0.528	20 (5)	109 (95.6)	126 (95.4)	0.941
Baseline antiplatelet, *N* (%)	29 (19.7)	52 (22.4)	0.534	15 (3.8)	25 (21.8)	34 (25.7)	0.533
Baseline anticoagulation, *N* (%)	12 (8.2)	40 (17.2)	0.012	15 (3.8)	14 (12.2)	14 (10.6)	0.706
Admission SBP, mean (SD)	151 (25)	149 (29)	0.534	80 (20.3)	153.7 (39)	148.9 (31)	0.272
Admission DBP, mean (SD)	85 (16)	83 (20)	0.344	81 (20.5)	85.8 (24)	83.5 (22)	0.437
Blood Glucose, mean (SD)	8 (3)	8 (3)	0.613	111 (28.1)	8 (3)	8 (4.0)	0.712
Admission NIHSS, mean(SD)	12 (10)	17 (13)	0.001	52 (13.2)	14 (14)	13 (11)	0.569
PC-ASPECTS, median (IQR)	8 (3)	8 (4)	0.013	22 (5.58)	8 (3)	8 (3)	1.000
Etiology, *N* (%)							
Atheroma	42 (29.2)	56 (24.1)			35 (30.7)	33 (25)	
Cardioembolic	47 (32.6)	73 (31.5)			40 (35)	50 (37.8)	
Dissection	4 (2.8)	19 (8.2)			2 (1.7)	9 (7.8)	
Other/Unknown	51 (35.4)	84 (36.2)	0.160	18 (4.5)	37 (32.4)	40 (30.3)	0.340
Admission Mode, *N* (%)							
Mothership	66 (44.0)	93 (39.2)			45 (39.4)	65 (49.2)	
Drip and Ship	72 (48.0)	91 (38.4)			59 (51.7)	48 (36.3)	
Intra-hospital/Other	12 (8.0)	53 (22.4)	0.001	7 (1.7)	10 (8.7)	19 (14.3)	0.162
General Anesthesia, *N* (%)	88 (59.1)	168 (69.4)	0.036	3 (0.7)	68 (59.6)	80 (60.6)	0.914
1st line EVT strategy, *N* (%)							
Stentriever	6 (4.3)	10 (4.3)			7 (6.1)	5 (3.7)	
Aspiration	89 (64.5)	153 (65.1)			77 (67.5)	85 (64.3)	
Stentriever and Aspiration	43 (31.2)	72 (30.6)	0.993	21 (5.3)	30 (26.3)	42 (31.8)	0.483
Rescue therapy, *N* (%)							
None	109 (74.1)	148 (61.9)			78 (68.4)	95 (71.9)	
Stenting	13 (8.8)	21 (8.8)			13 (11.4)	8 (6)	
Angioplasty only	15 (10.2)	20 (8.4)			13 (11.4)	7 (5.3)	
Pharmacological Treatment	10 (6.8)	50 (20.9)	0.003	8 (2)	10 (8.7)	22 (16.6)	0.589
Time from symptom onset to puncture (min), median (IQR)	270 (156)	318 (244)	0.007	18 (4.5)	306 (191)	300.0 (230)	0.828

*After multiple imputations and matched with an Inverse Propensity Score (IPS) model including age, sex, hypercholesterolemia, diabetes, baseline mRS, anticoagulation, admission mode, rescue therapy, baseline PC-ASPECTS, baseline NIHSS, general anesthesia, and time from symptom onset to puncture. For the outcome variables the missing values were the following: Number of passes (92/394, 23.3%), rescue therapy (7/394, 1.7%), mTICI post EVT (19/394, 4.8%), ΔNIHSS (41/394, 10.4%), 90-day mRS (26/394, 6.6%), parenchymal hematoma (88/394, 22.3%), symptomatic intracranial hemorrhage (69/394, 17.5%).

TABLE 2. Outcomes for the Inverse Propensity Matched Cohort of Patients with Vertebrobasilar Artery Occlusions

	IVT + EVT ($N = 114$)	EVT alone ($N = 132$)	Univariate			Multivariate*		
			OR	95% CI	*p*-value	OR	95% CI	*p*-Value
No. of passes ≤2, *n* (%)	68 (76.4)	79 (76.0)	1.03	0.51–2.07	0.942	1.03	0.49–2.14	0.946
mTICI 2b-3, *n* (%)	105 (93.8)	118 (94.4)	0.93	0.22–3.92	0.926	1.00	0.27–3.73	0.998
mTICI 3, *n* (%)	72 (64.3)	90 (72.0)	0.71	0.38–1.32	0.281	0.71	0.38–1.31	0.274
NIHSS at 24 h, median (IQR)	5 (16)	4 (19)			0.702			0.292
mRS 0–3 at 90 days, *n* (%)	65 (59.6)	70 (55.1)	1.18	0.67–2.09	0.562	1.23	0.67–2.25	0.512
mRS 0–2 at 90 days, *n* (%)	53 (48.6)	55 (43.3)	1.28	0.73–2.24	0.396	1.53	0.82–2.85	0.186
Shift Analysis (1-point mRS improvement)			0.76	0.47–1.23	0.262	0.72	0.44–1.18	0.192
Complications, *n* (%)	2 (1.8)	3 (6.8)	0.20	0.04–0.96	0.044	0.19	0.04–0.98	0.047
Perforations, *n* (%)	0 (0.0)	3 (2.2)						
ENT, *n* (%)	1 (0.9)	2 (1.5)						
Dissections, *n* (%)	1 (0.9)	4 (3.0)						
Rescue Therapy, *n* (%)	20 (17.5)	22 (16.6)	1.06	0.53–2.12	0.877	1.05	0.52–2.12	0.880
Aspirin	12 (10.5)	13 (9.8)						
Anti-GPIIbIIIa	6 (5.2)	6 (4.5)						
Intra-arterial rt-PA	0 (0.0)	7 (5.3)						
Mortality at 90 days, *n* (%)	27 (24.8)	41 (32.3)	0.68	0.36–1.27	0.222	0.63	0.33–1.23	0.179
PH Hemorrhage, *n* (%)	2 (2.1)	3 (2.8)	0.86	0.18–3.98	0.842	0.85	0.18–4.15	0.843
Symptomatic Intracranial Hemorrhage, *n* (%)	2 (2.0)	6 (5.1)	0.40	0.10–1.60	0.193	0.40	0.09–1.77	0.229

Note: Populations matched for age, sex, hypercholesterolemia, diabetes, baseline mRS, anticoagulation, admission mode, rescue therapy, baseline NIHSS, baseline PC-ASPECTS, general anesthesia, time from symptom onset to puncture.

Abbreviations: ENT, embolization in a new territory; EVT, endovascular therapy; IVT, intravenous thrombolytics; mRS, modified Rankin scale; mTICI, modified Treatment in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; PH, parenchymal hemorrhage; rt-PA, recombinant tissue plasminogen activator.

*Adjusted for age, baseline NIHSS, baseline PC-ASPECTS, time from symptom onset to puncture.

atherosclerosis) is displayed in Table S4. In the subgroup of patients without intracranial atherosclerosis, IVT prior to EVT was associated with improved adjusted odds of good functional outcome (aOR = 2.34, 95% CI, 1.12–4.86, $p = 0.021$), decreased mortality (aOR = 0.36, 95% CI, 0.17–0.78, $p = 0.009$) and improvement in adjusted odds of 1-point mRS shift (aOR = 0.53, 95% CI, 0.31–0.91, $p = 0.021$). In contrast, no effect of IVT was detected in the subgroup of patients with intracranial atherosclerosis.

Discussion

In this propensity-score matched analysis, EVT alone resulted in similar rates of good functional outcome, functional independence, and successful reperfusion compared to IVT + EVT. Safety outcomes also did not differ between the two groups.

Several randomized trials have recently evaluated the non-inferiority and superiority of EVT alone versus IVT + EVT in patients suffering from an AIS due to an anterior LVO, with conflicting results.[6–11] Among the numerous

arguments raised against IVT use before EVT for patients admitted in an endovascular-capable center, the main ones include higher risks of hemorrhagic complications, risk of thrombus fragmentation and migration to new territories, a relatively poor efficacy in terms of recanalization, potential time delays for EVT, and cost of the medication in some countries, among others.[13,14] However, these arguments may not be entirely relevant to posterior circulation strokes, as these patients show particularly low rates of hemorrhagic complications compared to anterior circulation strokes.[1–3,15] The relatively recent demonstration of the efficacy of EVT compared to medical management alone in LVO of the posterior circulation explains the absence of randomized trials in this setting.

Recent observational studies evaluating this question have also led to conflicting results. Nappini et al. showed similar rates of recanalization, symptomatic intracranial hemorrhages, and functional outcome at 3 months between EVT alone and IVT + EVT patients, but a shift toward better outcomes in IVT + EVT patients treated within the first 6 h.[16] More recently, Siow et al. also found similar rates of favorable outcome (mRS 0–3 at 3 months), symptomatic intracranial hemorrhage and mortality between EVT alone and IVT + EVT patients, but a potential benefit of IVT before EVT in patients with atherosclerotic disease as the underlying cause of AIS.[17] In contrast, Nie et al. recently found worse functional outcomes in the EVT alone group,[18] a finding that was confirmed in two recent meta-analysis.[18,19] However, these observational studies comprise several important limitations mainly inherent to their design, which include a small number of patients included, and more importantly the absence of matched analysis, making a head-to-head comparison of the EVT alone and IVT + EVT groups challenging. Indeed, the direct EVT group of these studies was often more severe than the IVT + EVT, with longer symptom onset to reperfusion, higher baseline NIHSS, increased use of antiplatelet or anticoagulant at baseline, all of which may have biased the results, despite quality multivariate analyses.

As discussed above, the management of AIS due to BAO includes several aspects that are distinct from anterior LVO AIS. From a technical perspective, EVT of posterior LVO are often more complex, requiring special skills due to the more frequent use of rescue therapies including intracranial balloon angioplasty, stenting with or without adjuvant intravenous or intra-arterial antiplatelet therapy in case of intracranial atherosclerosis stenosis. In the BASICS, ATTENTION, and BAOCHE trials, EVT alone was associated with an increased rates of ICH compared to the medical group,[1–3] a finding that was not observed in the HERMES meta-analysis of anterior LVO trials,[15,20] which might be explained by these technical specificities. This is highlighted by the higher rates of procedural complications in the ATTENTION and BAOCHE trials compared to anterior LVO randomized trials, reaching 14% of procedural complications (6 arterial dissections, 5 perforations, one of which was fatal) in the ATTENTION trial,[1] and 11% in the BAOCHE trial.[2] In this specific situation, it is therefore possible that IVT use prior to EVT may add some difficulty to the procedure, making the margin for error even smaller despite more dangerous intracranial maneuvers (ie, perforation, dissection), and increasing the risk of complications if intravenous antiplatelet are used on top of IVT. That said, patients treated with IVT before EVT seemed to receive significantly less pharmacological treatments (intravenous antiplatelet during EVT) compared to EVT alone patients before matching, suggesting a potential effect of IVT that has to be evaluated in dedicated studies. In addition, we found decreased odds of mortality at 90 days in the IVT + EVT group compared to the EVT alone group in patients transferred from a primary stroke center (Table S3) and increased odds of good functional outcome in the IVT + EVT group in patients without intracranial atherosclerosis (Table S4). However, the small number of patients included in these analyses is a strong limitation and further studies will be needed before conclusions can be drawn in these populations.

Second, the time window for reperfusion therapies in BAO seems to be longer from that of the anterior circulation, because of distinct and specific anatomical features of the posterior circulation (highly developed persistent collateral arterial network, reverse filling of the basilar artery, flow siding the clot, nicely reviewed by Lindsberg et al.[21]). These anatomical features may sustain patency of arterial perforators,[21] allowing local perfusion and preventing rapid necrosis despite arterial occlusion. Considering its low rate of efficacy in terms of recanalization in BAO,[14] the effect of IVT may be driven by targeting downstream microcirculation thrombosis, as recently demonstrated in anterior LVO.[22–25] However, the specific anatomical features of the posterior circulation may lead to different effects of IVT on the local microcirculation as compared to the anterior circulation, and further preclinical and clinical studies are needed to assess the relationship between thrombo-inflammation, microcirculatory perfusion impairments and IVT in posterior AIS.

Contrary to our hypothesis, we did not find decreased rates of parenchymal hemorrhages ($p = 0.21$) and symptomatic ICH ($p = 0.46$) in the EVT alone group compared to the IVT + EVT. Interestingly, rates of symptomatic ICH were also increased in the EVT alone group of the ATTENTION and BAOCHE trials (5%

and 6%) compared to the medical group, despite low use of IVT (31% and 14% in the EVT group, respectively). Importantly, the rates of hemorrhagic complications were not increased compared to the medical group in the anterior LVO trials, which suggest different pathophysiological mechanisms for hemorrhagic complications in posterior LVO compared to anterior LVO. Indeed, the fact that reperfusion rates after EVT for both anterior or posterior LVO are similar (90%)[1,26] do not plead for reperfusion-related hemorrhagic complications, but rather towards hemorrhagic complications driven by the procedure itself, possibly explained by the specific features of the posterior circulation discussed above. In a histopathological study analyzing 1,362 post-mortem large artery segments, Roth et al. demonstrated that posterior brain arteries differed histologically from anterior arteries, with thinner wall, increased elastin loss and less collagen deposition in older age.[27] In addition, differences in the embryological origin of the cells composing the arterial wall (ie, smooth muscle cells, pericytes) between the anterior and posterior vessels have been described (ie, mesoderm or neural crest cells), and may partly explained the discrepancies observed between anterior and posterior arteries.[28,29] Previous histological studies also described acute damage to the vessel wall caused by either stent retrievers or thrombo-aspiration, with endothelium loss, thickening of the internal elastic lamina, degeneration of the lamina media and adventitia.[30–33] Combined with increased use of rescue therapies, these data may thus explain the increased rates of hemorrhagic complications in the endovascular treatment of posterior LVO compared to the anterior circulation, and future randomized trials evaluating this question will be needed to comprehensively understand the effect of IVT before EVT in this situation.

This study has several strengths, which include its large population, multicenter design, and its propensity score matched analysis to address the significant differences between the two populations (ie, EVT alone versus IVT + EVT). However, several limitations should be discussed. First, despite the propensity score analysis, this study is observational and may lead to several confounding biases in the analysis. Second, the propensity score matching analyses only corrects for the observed confounders and therefore, several unobserved confounders and variables could influence the results of the study. Third, the propensity score matching analyses also significantly reduced the size of the studied population, altogether resulting in a loss of power in the analyses. Fourth, final angiographies after EVT were not systematically reviewed by a central core lab and mTICI were adjudicated by the operator in charge. Fifth, further studies will be needed to assess the impact of pharmacological rescue therapies in addition to IVT and EVT on the occurrence of ICH. Indeed, given the small number of patients receiving these treatments, multivariate analyses could not be performed. Finally, the patients included in this study were mostly Caucasians and further studies will be needed to confirm our data in Asian populations.

Conclusion

In this matched analysis, EVT alone seemed to lead to similar rates of good functional outcome and functional independence, and similar safety outcomes compared to IVT + EVT. However, the observational nature of the study, our moderate sample size and the likelihood of bias should be considered before generalizing these results to everyday practice. Randomized controlled trials are needed to specifically investigate this question in the setting of posterior circulation LVO.

Author Contributions

B.M., S.F., M.M., B.G., J.M.O. contributed to the conception and design of the study. B.M., S.F., M.M., B.L., G.M., I.S., S.R., C.C., A.V., B.G., J.M.O. contributed to the acquisition and analysis of data. B.M., S.F., B.G., M.M., J.M.O. contributed to drafting the text and preparing the figures. Supplementary Table S5 displayed the investigators of the ETIS registry.

Potential Conflicts of Interest

J.M.O. declares consulting activities with Abbvie, Acticor and Bioxodes; speaking fees from BMS, Boerhinger Ingelheim; SF 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 and is the primary investigator of the TITAN, DIRECT ANGIO, and IA-RESCUE trial, and consulting fees from Air Liquide, MIVI, Medtronic, Microvention, and Penumbra. M.M. declares consulting fees from Boerhinger Ingelheim, Air Liquide, Acticor Biotech, and Amgen. S.R. declares contracts from Boerhinger Ingelheim France, Bristol-Myers Squibb, Pfizer SAS.

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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