

Effectiveness and Safety of IV Thrombolysis Before Hospital Transfer for Thrombectomy in Patients With Basilar Artery Occlusion

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Abstract

Background and Objectives

The benefit of IV thrombolysis (IVT) before endovascular therapy (EVT) in acute ischemic stroke patients with basilar artery occlusion (BAO) remains unclear. Most existing studies have focused on patients directly admitted to comprehensive stroke centers (CSCs), where EVT is readily available. Our objective was to evaluate the effectiveness and safety of IVT initiated before interhospital transfer in patients with BAO initially admitted to a primary stroke center (PSC).

Methods

We analyzed data from 3 prospectively collected cohorts of patients with BAO transferred from a PSC to a CSC (Rothschild Foundation Hospital, Montpellier University Hospital, Stanford Hospital) for EVT consideration, regardless of whether EVT was ultimately performed. The primary effectiveness outcome was favorable 3-month functional outcome (modified Rankin Scale [mRS] score 0–2). Secondary effectiveness outcomes included excellent outcome (mRS score 0–1) and basilar artery recanalization during transfer (modified Thrombolysis In Cerebral Infarction score 2a–3 at CSC arrival). Safety outcomes included 3-month mortality and any intracerebral hemorrhage (ICH) on 24-hour imaging. The relationship between outcomes and IVT was assessed using multivariable logistic regression adjusting for relevant confounders.

Results

A total of 230 patients were included (median age, 71 years [interquartile range (IQR) 60–78]; 47% female). Ninety (39%) received IVT before transfer. IVT was mostly withheld because of presentation beyond 4.5 hours (61%) or anticoagulant use (14%). The median NIHSS score at the PSC was 14 (IQR 7–24). In multivariable analyses adjusted for the main confounders, IVT was independently associated with favorable 3-month outcome (39% vs 24%, adjusted odds ratio [aOR] 2.02, 95% CI 1.03–3.97, $p = 0.04$). Regarding secondary outcomes, IVT was associated with basilar recanalization during transfer (aOR 23.7, 95% CI 6.9–81.3, $p < 0.001$) while mortality at 90 days (aOR 1.12, 95% CI 0.58–2.18) and any ICH at 24 hours (aOR 1.55, 95% CI 0.77–3.1) did not significantly differ between IVT-treated and non-IVT-treated patients.

Discussion

In patients with BAO transferred for thrombectomy consideration, IVT before transfer was associated with improved recanalization and functional outcomes, without significant safety

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Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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Supplementary Material

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Coinvestigators are listed in the Appendix at the end of the article.

Glossary

AIS = acute ischemic stroke; **BAO** = basilar artery occlusion; **BMT** = best medical treatment; **CSC** = comprehensive stroke center; **DSA** = digital subtraction arteriography; **ESMINT** = European Society for Minimally Invasive Neurological Therapy; **ESO** = European Stroke Organisation; **EVT** = endovascular therapy; **ICH** = intracerebral hemorrhage; **IVT** = IV thrombolysis; **LVO** = large vessel occlusion; **mRS** = modified Rankin Scale; **mTICI** = modified Thrombolysis In Cerebral Infarction; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **pc-ASPECTS** = Posterior Circulation Alberta Stroke Program Early CT Score; **PH** = parenchymal hematoma; **PSC** = primary stroke center; **RCT** = randomized controlled trial.

concerns. However, IVT was administered in only 39% of patients, suggesting a potential need to broaden IVT eligibility criteria in this setting. These findings require confirmation in future studies, given the limited sample size and observational design.

Classification of Evidence

This study provides Class III evidence that in patients with BAO, administering IVT before hospital transfer for thrombectomy is safe and associated with a favorable functional outcome at 3 months.

Introduction

Basilar artery occlusion (BAO) accounts for only 5% of acute ischemic strokes (AISs) with large vessel occlusion (LVO),¹ but it is associated with high rates of mortality and severe disability.^{2,3} Two recent randomized controlled trials (RCTs) have shown that endovascular therapy (EVT), in addition to best medical treatment (BMT), improves functional outcomes in patients with BAO up to 24 hours after symptom onset, compared with BMT alone.²⁻⁵ However, the role of IV thrombolysis (IVT) before EVT in patients with BAO remains uncertain. The RCTs comparing EVT with or without preceding IVT excluded patients with BAO, except for the DIRECT-SAFE trial (A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy), which included only 19 patients with BAO, thus precluding definitive conclusions in this population.^{6,7} Observational studies comparing direct EVT with IVT plus EVT in patients with BAO have yielded conflicting results: some suggested a benefit of IVT on clinical outcomes⁸⁻¹¹ while others found no significant difference.¹²⁻¹⁷ However, these studies mostly included patients treated with IVT at comprehensive stroke centers (CSCs), where EVT was rapidly initiated—thereby narrowing the window for IVT effectiveness.¹⁸

By contrast, many patients with BAO in the real-world setting are first evaluated at primary stroke centers (PSCs),¹⁹ where IVT is administered before transfer for EVT.¹⁸ These interhospital transfer durations often exceed 1 hour, allowing more time for IVT to induce recanalization before the EVT procedure.¹⁸ Moreover, all of these studies were based on EVT registries, thus restricting their analysis to patients who ultimately underwent EVT.⁸⁻¹⁶ This introduced a potential selection bias by excluding patients who were not treated by EVT

because of either recanalization or clinical improvement, outcomes that have been strongly associated with IVT use before transfer in anterior LVO.^{18,20} These studies may thus have underestimated the full benefit of IVT in BAO.

The impact of IVT in patients with BAO initially diagnosed at a PSC and transferred to a CSC for consideration of EVT is not established. This study used data from 3 large, prospectively collected cohorts that included all transferred patients for EVT, regardless of whether EVT was eventually performed. The primary research question was whether IVT administered at the PSC before interhospital transfer is independently associated with improved clinical outcomes in patients with BAO. Secondary research questions included its association with vessel recanalization during transfer and with safety outcomes, namely 3-month mortality and intracerebral hemorrhage (ICH).

Methods

Study Design, Population, and Data Sources

This international retrospective study combined data from 3 prospectively collected cohorts of patients with AIS due to BAO who were consecutively transferred from a PSC to one of 3 CSCs for consideration of EVT: Rothschild Foundation Hospital (Paris, France), Montpellier University Hospital (Montpellier, France), and Stanford Hospital (Stanford, CA).

Patients were included if they met the following criteria: (1) initial admission at a PSC where a CT with CT angiography or MRI with MR angiography confirmed BAO; (2) subsequent transfer to a CSC for consideration of EVT, regardless of whether EVT was eventually attempted. Inclusion dates were January 2017 to February 2024 for Paris, March 2016 to

October 2023 for Montpellier, and December 2016 to October 2023 for Stanford.

Treatment Protocols and Indication of Transfer

Given the long study period, local protocols evolved over time but followed consistent principles across the participating primary PSCs.

IVT was administered within 4.5 hours of symptom onset, in the absence of contraindication. Since mid-2018, based on accumulating evidence, primarily from anterior circulation stroke studies,^{21,22} IVT was also used in selected patients with unknown symptom onset and FLAIR-negative MRI, mainly in French centers where MRI is the preferred imaging. It is important to note that these practices preceded the publication of the most recent European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines,³ which now formally support the use of IVT up to 12–24 hours in selected cases of posterior circulation stroke.

Regarding transfer decision, given that early clinical deterioration is common in patients with BAO,²³ a uniform protocol was applied across all 3 participating CSCs: all patients with acute BAO with even mild deficits at the PSC were transferred to the CSC for EVT consideration. Even in patients with severe neurologic impairment or rapid clinical worsening at the PSC, transfer was usually pursued, with intubation and sedation performed beforehand to ensure safe transport when needed. In rare cases, such as very early death or formal decisions to withdraw care, transfer was not performed. In patients who were not intubated before transfer, intubation could be performed on arrival at the CSC before EVT, particularly for procedural safety or in the event of clinical worsening during transport.

EVT was ultimately performed at the CSC in patients with moderate-to-severe stroke (typically NIH Stroke Scale [NIHSS] score at CSC >5). After EVT, extubation was not systematically performed during the first 24–48 hours and was instead guided by local intensive care unit protocols. The decision to maintain intubation was influenced by multiple factors, including initial stroke severity, hemodynamic stability, and respiratory status at the discretion of the treating team.

Standard Protocol Approvals, Registrations, and Patient Consents

Our analysis was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria for observational studies.²⁴ The research was approved by the Stanford review board for the US cohort and by the Rothchild Foundation Hospital review board for the French cohort. In the US cohort, each participant or a surrogate provided verbal informed consent. In the French cohort, the requirement for written informed consent was waived because

the study was limited to retrospective analysis of anonymized data collected during routine care.

Clinical and Treatment Data

Variables collected included age, sex, prestroke modified Rankin Scale (mRS) score, vascular risk factors, history of stroke, known symptom onset, last seen well (defined as the last moment the patient was observed without neurologic deficit, in line with definitions used in major BAO trials^{4,5,25}) and symptom onset times, NIHSS score at the PSC, IVT use and agent (alteplase or tenecteplase) or reason for withholding IVT at the PSC, time from symptom onset to IVT, EVT realization or reason for withholding EVT at the CSC, intubation at 24 hours, stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment classification,²⁶ and 3-month mRS score, assessed by a stroke neurologist or a trained research nurse, either during an in-person visit or through phone interview.

Radiologic Data

All included patients underwent either MRI or CT on admission at the PSC. MRI was the routine first-line imaging in all French PSCs, with a standardized protocol at each institution (which systematically included diffusion-weighted imaging, T2*, and MR angiography). Noncontrast CT with CT angiography was the routine first-line imaging technique for EVT candidates in all PSCs in the US cohort. On arrival at CSC, patients underwent post-transfer imaging (MRI with MR angiography or CT with CT angiography) or directly went to the angiosuite for digital subtraction arteriography (DSA), bypassing noninvasive imaging; this decision was left to the discretion of the treating on-call physicians. A follow-up CT or MRI was also performed 24–36 hours later.

At each CSC, 1 reader (F.C., S.L., or A.T.S.) was assigned to review all PSC and CSC imaging, blinded to clinical data. To ensure homogeneity in radiologic evaluation, all readers underwent a training session using an imaging tutorial that defined each variable with multiple examples. In case of doubt concerning data classification, the situation was resolved by consensus with the other readers. The following variables were collected: (1) BAO site assessed on MR angiography or CT angiography at PSC (the basilar artery was divided into 2 equal segments, with proximal occlusion occurring before the midpoint and distal occlusion occurring beyond); (2) extent of ischemic core, assessed using the Posterior Circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) on PSC noncontrast CT or diffusion-weighted imaging^{27,28}; (3) interhospital arterial recanalization, assessed by head-to-head comparison of the PSC angiography (MR angiography or CT angiography) and the post-transfer CSC angiography (first run of the DSA, MR angiography, or CT angiography), rated using a modified Thrombolysis In Cerebral Infarction (mTICI) score²⁹ (for patients with control noninvasive arterial imaging on CSC arrival immediately followed by DSA, the DSA was used for recanalization assessment); (4) final mTICI score for patients who underwent EVT; (5) evidence

of any ICH on 24–36-hour follow-up noncontrast CT or T2* MRI, including hemorrhagic infarction and parenchymal hematoma (PH) according to the European Cooperative Acute Stroke Study II classification³⁰ and subarachnoid and intraventricular hemorrhage.

Outcomes

The primary effectiveness outcome was favorable functional outcome, defined as an mRS score of 0–2 at 3 months. Secondary outcomes were interhospital recanalization, defined as mTICI grades 2a, 2b, or 3,²⁹ and excellent 3-month functional outcome, defined as an mRS score 0–1. Safety outcomes included 3-month mortality and any ICH and PH grade 1 or 2 assessed on 24-hour follow-up imaging.

Statistical Analysis

Categorical variables were expressed as counts (percentages) and continuous variables as medians (Q1–Q3). Patients were divided into 2 groups based on IVT administration at the PSC. Between-group comparisons were performed using the Student *t* test or the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables, as appropriate.

Univariate associations between IVT use and study outcomes were assessed using logistic regression. The association between IVT and favorable 3-month outcome was further examined using multivariable binary logistic regression. Variables with a *p* value <0.10 in univariate analysis were considered eligible for inclusion as covariates in the multivariable model. Variables known to be strongly associated with clinical outcomes in the literature^{8–17}—namely age, prestroke mRS score, pc-ASPECTS, NIHSS score at PSC, and time from symptom onset to CSC imaging—were also included a priori. Time from symptom onset to CSC imaging was preferred over time to puncture because the latter was unavailable for patients who did not undergo EVT. Variables were retained in the final model if *p* < 0.10. To prevent model overfitting,³¹ the recruiting center was not included in the primary analysis but was added in sensitivity analyses for the primary outcome. Interaction terms were also tested between IVT and occlusion site and between IVT and baseline imaging type (CT vs MRI) for the primary outcome.

A similar approach was applied for secondary outcomes. For 3-month mortality, covariates were identical to those used for the favorable 3-month outcome. Regarding the other secondary outcomes, owing to the relatively small number of events, a more restrictive set of covariates was used to minimize the risk of overfitting. For excellent outcome (mRS score 0–1), included covariates were age, prestroke mRS score, pc-ASPECTS, and NIHSS score at PSC; for interhospital recanalization, included covariates were BAO site and PSC-to-CSC imaging time; and for any ICH, included covariates were NIHSS score at PSC, pc-ASPECTS, and final mTICI score 2b–3.

Considering the very low number of missing data, analyses were conducted on available cases (i.e., patients with

complete data for the covariates included in each model), without imputation. Results were reported as odds ratios (ORs) with their 95% CIs. For PH, a Fisher exact test was used for univariate analysis, and multivariable analysis was not performed because of the very low number of observed events.

All statistical tests were 2-sided, and statistical significance was set at *p* < 0.05. Statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY).

Data Availability

The data supporting the study findings are available on reasonable request.

Results

Study Population

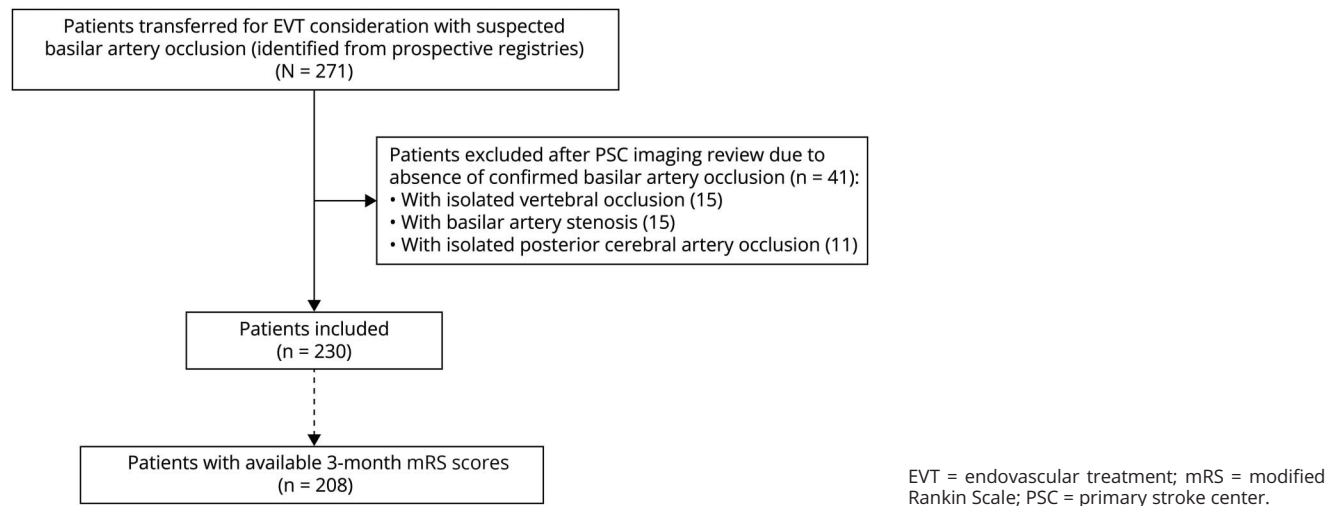
A total of 271 patients were initially identified from prospective registries as transferred for EVT consideration because of suspected BAO. After PSC imaging review, 41 patients were excluded because of absence of confirmed BAO, resulting in 230 patients included in the analysis. The patient selection process is illustrated in Figure 1. The median age was 71 years (interquartile range [IQR] 60–78), 53% of patients were male, and the median NIHSS score at the PSC was 14 (IQR 7–24). The median time from last seen well to PSC imaging was 181 minutes (IQR 114–395). Ninety (39%) patients received IVT at the PSC before transfer (alteplase in 87 [97%] and tenecteplase in 3 [3%]) while 140 (61%) did not; reasons for withholding IVT are presented in Figure 2. The time from symptom onset to IVT was 179 minutes (IQR 132–237).

Patient characteristics according to IVT use are provided in Table 1. Patients treated with IVT had a lower rate of hypertension, more frequently witnessed symptom onset, shorter times from last seen well to PSC imaging and from symptom onset to CSC imaging, and higher frequency of distal basilar occlusion compared with patients not treated with IVT. Other baseline characteristics, including age, sex, and pc-ASPECTS and NIHSS score, were similar between groups. On CSC admission, EVT was less frequently performed in the IVT group. At 24 hours, 28 patients (31%) treated with IVT remained intubated, compared with 54 patients (39%) not treated with IVT (*p* = 0.25).

Primary Effectiveness Outcome (3-Month mRS Score 0–2)

The 3-month mRS score was available in 208 of 230 patients (90%). Of note, missing 3-month mRS data were more frequent in the no-IVT group (19/140, 13.6%) compared with the IVT group (3/90, 3.3%), indicating significant differential missingness (*p* = 0.01).

The distribution of mRS scores at 3 months according to IVT use is shown in Figure 3. A favorable outcome (mRS

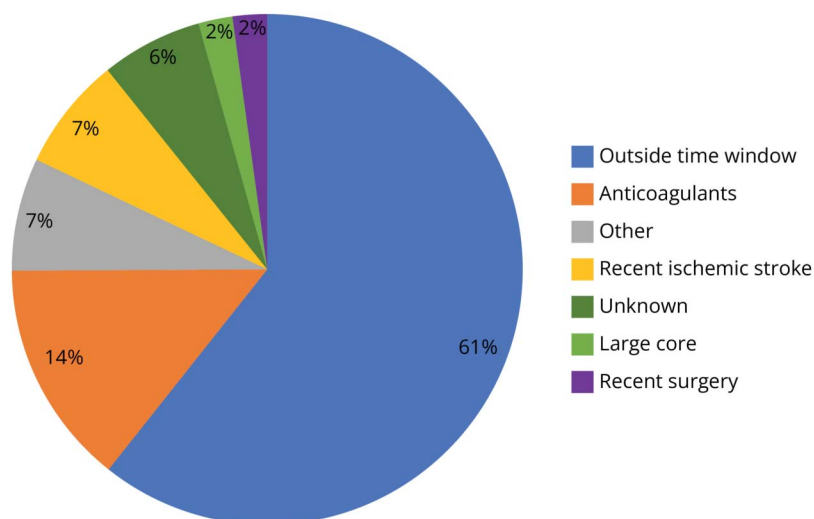
Figure 1 Flowchart of Patient Selection

score 0–2) was achieved in 34 of 87 IVT-treated patients (39%), vs 29 of 121 patients (24%) who did not receive IVT. In univariate logistic regression, IVT use was associated with higher odds of favorable outcome (OR 2.04, 95% CI 1.12–3.71, $p = 0.02$). This association remained significant after adjustment for confounders (adjusted OR 2.02, 95% CI 1.03–3.97, $p = 0.04$, Table 2) and in the sensitivity analysis including study center as an additional covariate in the multivariable model (adjusted OR 2.12, 95% CI 1.06–4.26, $p = 0.03$). No significant interaction was found between IVT and occlusion site (distal vs proximal) (p for interaction = 0.11), or between IVT and baseline imaging modality (CT vs MRI) (p for interaction = 0.67),

suggesting that the association between IVT and outcome was similar across occlusion sites and independent of the imaging modality used at baseline.

Secondary Effectiveness and Safety Outcomes

Results regarding secondary outcomes are presented in Table 3. Rates of successful recanalization during inter-hospital transfer were significantly higher in the IVT group, in both univariate (36% vs 2%, OR 25.5, 95% CI 7.5–86.5, $p < 0.001$) and multivariable (adjusted OR 23.7, 95% CI 6.9–81.3, $p < 0.001$) analyses. Details on persistent occlusion site and recanalization status at CSC arrival are provided in eTable 1. PH was more frequent in IVT-treated

Figure 2 Reasons for Withholding IV Thrombolysis Before Interhospital Transfer

Main reasons for not administering IV thrombolysis among the 140 patients who did not receive thrombolysis.

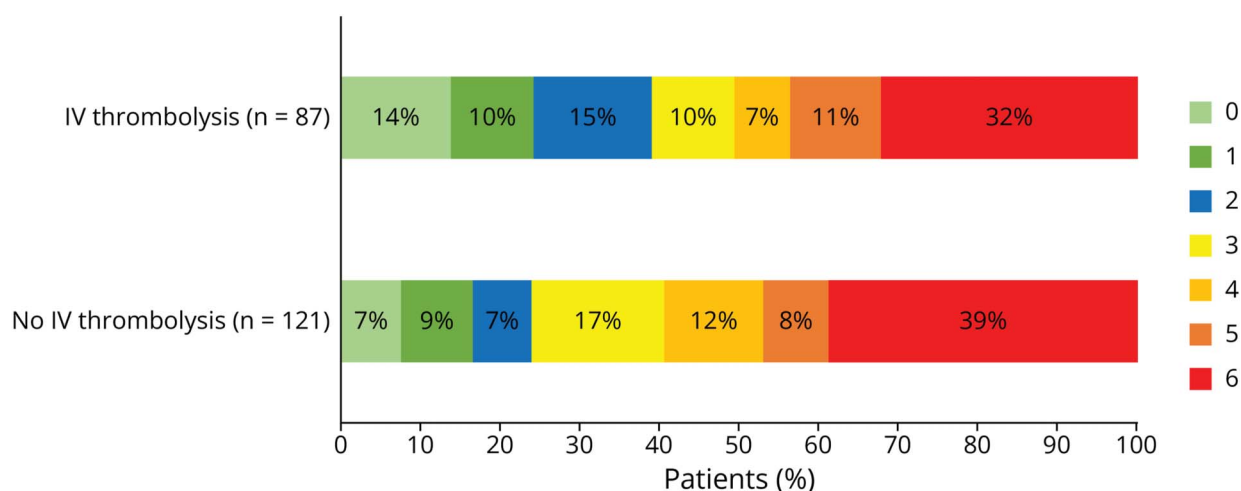
Table 1 Population Characteristics According to IVT Treatment

	Overall (n = 230)	IVT use (n = 90)	No IVT use (n = 140)	p Value
Age, y	71 (60–78)	70 (60–78)	71 (59–79)	0.84
Male	122 (53)	76 (54)	46 (51)	0.64
Prestroke mRS score 0–2	221 (96)	89 (99)	132 (94)	0.09
Hypertension	143 (62)	48 (53)	95 (68)	0.03
Diabetes	49 (21)	15 (17)	34 (24)	0.17
Current smoking	36 (16)	11 (12)	25 (18)	0.27
Dyslipidemia	56 (24)	19 (21)	37 (26)	0.43
History of stroke	37 (16)	12 (13)	25 (18)	0.36
CSC site				0.99
Paris	102 (44)	40 (44)	62 (44)	
Montpellier	76 (33)	30 (33)	46 (33)	
Stanford	52 (23)	20 (22)	32 (23)	
Clinical characteristics (PSC)				
Known symptom onset	152 (66)	71 (79)	81 (58)	0.001
NIHSS score	14 (7–24)	14 (7–23)	15 (5–25)	0.70
Imaging characteristics (PSC)				
Time from last seen well to imaging, min	181 (114–395)	144 (95–202)	272 (137–671)	<0.001
MRI as parenchymal imaging	138 (60)	58 (64)	80 (57)	0.27
pc-ASPECTS	8 (8–10)	8 (8–10)	8 (7–10)	0.54
Distal basilar occlusion	133 (58)	60 (67)	73 (52)	0.03
CSC arrival				
Time from PSC to CSC imaging, min	208 (156–259)	199 (160–244)	209 (154–309)	0.28
Time from symptom onset to CSC imaging, min	363 (283–496)	345 (273–398)	401 (288–555)	0.002
Explored by digital subtraction angiography	197 (86)	73 (81)	125 (89)	0.08
Endovascular treatment performed	177 (77)	59 (66)	118 (84)	0.001
Time from symptom onset to puncture, min	374 (279–536)	334 (265–400)	408 (290–592)	0.005
Final mTICI score 2b–3	157 (89)	57 (97)	100 (85)	0.02
Stroke etiology				0.23
Atheroma	70 (30)	21 (23)	49 (35)	
Cardioembolic	76 (33)	30 (33)	46 (33)	
Other	75 (33)	4 (4)	5 (4)	
Undetermined	9 (4)	35 (39)	40 (29)	

Abbreviations: CSC = comprehensive stroke center; IVT = IV thrombolysis; mRS = modified Rankin Scale; mTICI = modified Thrombolysis In Cerebral Infarction; NIHSS = NIH Stroke Scale; pc-ASPECTS = Posterior Circulation Alberta Stroke Program Early CT Score; PSC = primary stroke center. Categorical variables are expressed as n (%) and continuous variables as median (interquartile range). Missing data: NIHSS score (n = 1), time from PSC imaging to CSC imaging (n = 2), and time from symptom onset to CSC imaging (n = 3).

patients in univariate analysis (5% vs 0%, $p = 0.02$, Fisher exact test). Other secondary outcomes, including excellent functional outcome, 3-month mortality, and any ICH at

24 hours, did not significantly differ between IVT-treated and non-IVT-treated patients in either univariate or multivariable analysis.

Figure 3 Three-Month mRS Scores According to IV Thrombolysis Use Before Transfer

mRS = modified Rankin Scale.

Classification of Evidence

This study provides Class III evidence that in patients with BAO, administering IVT before hospital transfer for thrombectomy is safe and associated with a favorable functional outcome at 3 months.

Discussion

In this cohort of 230 patients with AIS due to BAO who were transferred from a PSC to a CSC for EVT consideration, 3 key findings emerged. First, IVT administration was associated with improved favorable 3-month outcomes, as well as an increased vessel recanalization rate during transfer. Second, no substantial safety concerns were identified with IVT use, with no increase in mortality rate or ICH on follow-up imaging, although PH was more prevalent in the IVT subgroup. Third, only 39% of the patients received IVT before transfer, most commonly withheld because of presentation beyond the 4.5-hour window or ongoing anticoagulation.

Regarding our primary outcomes, we reported a 39% rate of good outcomes in the IVT group and a 24% rate in the no-IVT group, rates broadly consistent with those reported in the literature.^{3,32} Our results suggesting a potential benefit of IVT on functional outcomes are particularly relevant, given the ongoing controversy surrounding the role of IVT before EVT in LVO in general, and more specifically in BAO. RCTs assessing bridging IVT in anterior circulation LVO have yielded conflicting results, and a meta-analysis did not establish noninferiority of EVT alone compared with IVT plus EVT.⁷ However, these trials included patients presenting directly at EVT centers,⁷ a setting where the potential benefit of IVT is less likely to be observed.¹⁸ Moreover, most excluded patients with BAO, except for the DIRECT-SAFE trial, which included only 19 patients with BAO.^{6,7} Available evidence in the posterior circulation is limited. Results on 3-month favorable outcome (mRS score 0–2) are conflicting in observational studies: some found IVT plus EVT to be beneficial^{8–11} while others did not.^{12–17} Meta-analyses of these studies have favored combined IVT and EVT

Table 2 Logistic Regression Models Showing Variables Associated With 3-Month mRS Score 0–2

Characteristics	Unadjusted OR (95% CI), <i>p</i> value	Adjusted OR (95% CI), <i>p</i> value
Prestroke mRS score (per 1 point)	0.34 (0.16–0.74), <i>p</i> = 0.006	0.37 (0.16–0.85), <i>p</i> = 0.02
Age (per 1 y)	0.96 (0.94–0.98), <i>p</i> = 0.001	0.97 (0.95–0.997), <i>p</i> = 0.03
NIHSS score at PSC (per 1 point)	0.94 (0.91–0.97), <i>p</i> < 0.001	0.94 (0.91–0.97), <i>p</i> < 0.001
pc-ASPECTS (per 1 point)	1.34 (1.07–1.67), <i>p</i> = 0.01	1.28 (0.995–1.65), <i>p</i> = 0.05
IV thrombolysis use	2.04 (1.12–3.71), <i>p</i> = 0.02	2.02 (1.03–3.97), <i>p</i> = 0.04

Abbreviations: mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds-ratio; pc-ASPECTS = Posterior Circulation Alberta Stroke Program Early CT Score.

Variables initially included in the multivariable model were age, prestroke mRS score, hypertension, pc-ASPECTS, basilar occlusion site, NIHSS score at primary stroke center, time from symptom onset to comprehensive stroke center, and endovascular treatment realization. Only variables with a *p* value < 0.10 were retained in the final model and presented here. Analyses were performed in patients with complete data for all variables retained in the multivariable model (*n* = 207; of the 230 patients included, 22 had missing 3-month mRS scores and 1 had missing baseline NIHSS scores).

Table 3 Secondary Outcomes According to IVT Treatment

	IVT (n = 90)	No IVT (n = 140)	Unadjusted binary logistic regression analysis OR (95% CI)	Adjusted binary logistic regression analysis OR (95% CI)
Secondary effectiveness outcomes				
Recanalization (mTICI score 2a–3) during transfer	32/89 (36)	3/139 (2)	25.5 (7.5–86.5)	23.7 (6.9–81.4)
3-mo mRS score 0–1	21/87 (24)	20/121 (17)	1.61 (0.81–3.2)	1.59 (0.76–3.3)
Secondary safety outcomes				
Any ICH at 24 h	20/84 (24)	22/134 (16)	1.59 (0.81–3.1)	1.56 (0.77–3.1)
Parenchymal hematoma	4/84 (5)	0/134 (0)	<i>p</i> = 0.02 ^a	—
3-mo mortality	28/87 (32)	47/121 (39)	0.75 (0.42–1.33)	1.12 (0.58–2.18)

Abbreviations: ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; mTICI = modified Thrombolysis In Cerebral Infarction; NIHSS = NIH Stroke Scale; pc-ASPECTS = Posterior Circulation Alberta Stroke Program Early CT Score; PSC = primary stroke center. Categorical variables are expressed as numbers/numbers of patients with available data (%).
^a For 24-hour parenchymal hematoma, a Fisher exact test was performed instead of a binary logistic regression analysis, because of the number of events. Regarding adjusted binary logistic regression analyses, only covariates with a *p* value <0.10 were retained in each model. Final covariates were as follows: basilar occlusion site for interhospital recanalization, prestroke mRS and NIHSS scores at PSC for 3-month mRS score 0–1, and NIHSS score at PSC for 24-hour any ICH. Covariates for 3-month death were as follows: age, hypertension, pc-ASPECTS, basilar occlusion site, NIHSS score at primary stroke center, and time from symptom onset to comprehensive stroke center.

for achieving 3-month mRS score 0–2.^{3,32,33} This led the ESO and ESMINT to suggest combined IVT and EVT treatment over direct EVT in their recent guidelines, with, however, a low quality of evidence and a weak strength of recommendation, acknowledging the low certainty of evidence.³ Our findings add valuable prospective data supporting this recommendation, particularly in the context of drip-and-ship pathways.

Our study differs from previous observational studies in 2 major ways. First, we included only patients initially admitted to a PSC, whereas previous studies mostly enrolled patients directly admitted to a CSC, with transferred patients representing only 29%–42% when reported.^{14,15,34}

Of interest, only 1 study specifically analyzed its subgroup of transferred patients, reporting a lower mortality among those treated with IVT before EVT, a difference that was not observed in the overall population.¹⁴ However, no significant differences in effectiveness or safety outcomes were reported between IVT and non-IVT patients in that subgroup, unlike in our study.¹⁴

Second, previous studies were exclusively based on EVT registries, limiting their analyses to patients who ultimately underwent EVT.^{8–16} This design introduces a major selection bias by excluding patients who recanalized or improved clinically during transfer, 2 outcomes strongly associated with IVT use in anterior circulation LVO and predictive of good functional outcomes at 3 months.^{18,20} By contrast, our study included all consecutive patients with BAO transferred for EVT consideration, regardless of whether thrombectomy was performed, providing a more comprehensive and unbiased evaluation of IVT’s potential benefits. Consistent with findings in anterior LVO,^{18,20} we observed a strong association between IVT and recanalization, with 35% of IVT-treated

patients achieving mTICI score 2a–3 recanalization during transfer compared with only 3% without IVT.

Regarding safety outcomes, we found no difference in the mortality rate or ICH between the IVT and non-IVT groups. PH occurred in 5% of patients in the IVT group vs 0% in the no-IVT group (*p* = 0.02). This rate is similar to that reported in 1 previous study, which found no difference between the patients treated and not treated with IVT (2.1% vs 2.8%, respectively).¹⁴ Unlike most previous studies,^{3,32,33} we did not report rates of symptomatic ICH because a significant proportion of patients in our cohort remained intubated at 24 hours, limiting the reliability of clinical assessment (notably, among the 4 patients with parenchymal hemorrhage, 3 were still intubated and the last one had a 5-point NIHSS increase). It is important to note that intubation at 24 hours was not necessarily related to neurologic deterioration after EVT, but often reflected institutional protocols for prolonged sedation and airway protection in the acute phase.

Only 39% of our cohort received IVT before transfer, consistent with the 37% rate reported in a recent meta-analysis of BAO studies.³² Given the observed benefit in our cohort, expanding IVT eligibility seems critical. In our series, 75% of IVT exclusions were due to 2 reasons, which represent key targets for future trials: presentation beyond the 4.5-hour window and previous anticoagulant therapy. For patients presenting beyond 4.5 hours, a recent meta-analysis of 8 randomized trials showed improved functional outcomes with IVT; however, patients with BAO were either excluded or underrepresented, and EVT was not performed.³⁵ The ETERNAL-LVO trial, in which patients within 24 hours were randomized to receive either tenecteplase or standard of care before EVT,³⁶ suggested a benefit specifically among transferred patients (unpublished data presented at the 2025 International Stroke Conference), but it did not involve BAO.

Finally, the EXPECTS trial showed improved outcomes with alteplase in patients with mild BAO treated between 4.5 and 24 hours, but EVT candidates were excluded, potentially explaining the unusually high rates of good outcomes observed.³⁷ An ongoing trial (NCT05105633) specifically evaluating late-window IVT in BAO should provide further evidence, although it does not focus on transferred patients. Of note, despite the lack of randomized evidence, European guidelines include an expert consensus statement suggesting the use of IVT rather than no IVT in patients with BAO in the late time window, without extensive ischemic changes in the posterior circulation.³ Regarding anticoagulated patients, a recent meta-analysis, although not focusing on patients with BAO, suggested that IVT could be considered a treatment option in patients with AIS with recent use of direct anticoagulation treatments because it was not associated with an increased risk of symptomatic ICH.³⁸

Finally, apart from broadening the IVT indications, using more efficient fibrinolytic therapies than alteplase, which was used in 97% of our patients, may be beneficial. One study found that tenecteplase was associated with higher recanalization rates than alteplase in patients with BAO, although most participants were directly admitted to CSCs.³⁹ Further studies specifically targeting transferred patients with BAO are warranted.

Our study has limitations. First, its observational design cannot fully eliminate residual confounding. Although multivariable models were adjusted for baseline imbalances, patients treated with IVT tended to have slightly more favorable profiles, including lower rates of hypertension and prestroke disability and shorter delays from last time seen well to imaging. These differences likely reflect clinical selection and IVT eligibility at the PSC level. Nonetheless, key prognostic variables such as age, initial NIHSS score, and pc-ASPECTS were well balanced between groups. Second, our population sample size was moderate, and only 63 patients achieved a favorable outcome. However, this is the only study specifically focused on transferred patients, and we believe that our results will be valuable for guiding future prospective studies or randomized controlled trials in this understudied population. Third, because patients were identified through registries maintained at the CSCs, our cohort only included those who were successfully transferred. Consequently, patients who died before transfer, or were deemed ineligible for EVT, were not captured, potentially introducing a selection bias. Fourth, 3-month mRS score was missing in 10% of patients, primarily because they did not attend the follow-up visit and could not be reached by phone, potentially introducing attrition bias. Differential missingness was observed, with a higher proportion of missing 3-month mRS data in the no-IVT group compared with the IVT group (13.6% vs 3.3%, $p = 0.01$). This could suggest that the observed benefit of IVT is underestimated, particularly if patients lost to follow-up in the no-IVT group had worse outcomes. However, because the reasons for missing follow-up remain unknown, we cannot exclude the opposite possibility, including that some of these patients may have had

better outcomes. This limitation also applies to the interpretation of secondary 3-month outcomes, particularly excellent outcome and mortality, which could similarly be affected by attrition bias. Fifth, generalizability to other settings should be made cautiously, and our results may not apply to settings where transfer durations are shorter. Sixth, pc-ASPECTS was assessed using either DWI or CT depending on center protocols and imaging availability; although this reflects real-world practice, it may introduce heterogeneity in pc-ASPECTS estimation. However, the absence of interaction between imaging modality and treatment effect supports the generalizability of our findings. Finally, because information on race and ethnicity was not collected, we were unable to evaluate potential differences in treatment effect across racial or ethnic groups. Given the predominance of Western European and North American patients in our cohort, our findings may not be generalizable to populations with different stroke pathophysiologies, such as Asian populations, where intracranial atherosclerosis is more prevalent.

Despite these limitations, our study provides compelling real-world evidence supporting the use of IVT before interhospital transfer in eligible patients with BAO, based on its association with improved clinical outcomes and early recanalization. By including all patients transferred for EVT consideration, regardless of final treatment, we address an important gap left by previous EVT registries and trials. Further randomized trials are needed to expand IVT eligibility in patients with BAO.

Author Contributions

S. Liebart: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.G. Lansberg: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Adwane: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. F. Charbonneau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Schwartz: major role in the acquisition of data. J.J. Heit: drafting/revision of the manuscript for content, including medical writing for content. M. Mlynash: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D. Sablot: drafting/revision of the manuscript for content, including medical writing for content. A. Wacongne: drafting/revision of the manuscript for content, including medical writing for content. J.-P. Desilles: drafting/revision of the manuscript for content, including medical writing for content. M. Obadia: drafting/revision of the manuscript for content, including medical writing for content. C. Henry: drafting/revision of the manuscript for content, including medical writing for content. E. Manchon: drafting/revision of the manuscript for content, including medical writing for content. C. Arquizan: drafting/revision of the manuscript for content, including medical

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Disclosure

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Continued

Appendix (continued)

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