Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

# Thrombolysis in Patients With Large-Vessel Occlusion Directly Admitted or Transferred to a Thrombectomy Center: A Population-Based Study

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**BACKGROUND:** Our goal is to evaluate whether the administration of thrombolytic treatment has varying effects on clinical and radiological outcomes in patients with large-vessel occlusion stroke, based on the type of stroke center where the treatment was given (thrombectomy-capable center versus local stroke center).

**METHODS:** We included patients with an acute ischemic large-vessel occlusion stroke who were directly admitted to thrombectomy-capable centers and treated with endovascular thrombectomy, or were transferred from local stroke centers as thrombectomy candidates, in Catalonia, Spain, between 2017 and 2021. The primary outcome was the shift analysis on the modified Rankin scale score at 90 days. Secondary outcomes included death at 90 days and the rate of parenchymal hemorrhage and successful reperfusion. Inverse-probability weighting clustered at the type of stroke center was used to estimate the effects.

**RESULTS:** The analysis included 2268 patients directly admitted to thrombectomy-capable centers, of whom 975 (49%) were treated with thrombolysis, and 938 patients transferred from local stroke centers, of whom 580 (66%) were treated with thrombolysis and 616 (67%) were treated with thrombectomy. Mean age was 72 (SD ±13) years, median National Institute of Health Stroke Scale score was 17 (interquartile range, 12–21), and 1363 patients were women (48%). Patients treated with intravenous thrombolysis were younger, had shorter time from onset to first image, higher Alberta Stroke Program Early Computed



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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/SVIN.122.000760

on behalf of the Catalan Stroke Code and Reperfusion Consortium (Cat-SCR Consortium)



*Stroke: Vascular and Interventional Neurology* is available at: www.ahajournals.org/journal/svin

Tomography Score, and lower rates of wake-up stroke, atrial fibrillation, and anticoagulation intake. Patients treated with thrombolysis had better functional outcome at 90 days, with no difference between patients directly admitted to thrombectomy-capable centers (adjusted common odds ratio [acOR], 1.50 [95% CI, 1.24–1.81]) and patients transferred from local stroke centers (acOR, 1.44 [95% CI, 1.04–2.01]). Patients treated with intravenous thrombolysis had lower death rate, higher rate of parenchymal hematoma, and similar rate of successful reperfusion, with no difference according to type of center ($P_{interaction}>0.1$).

**CONCLUSION:** Administration of intravenous thrombolysis in patients with a large-vessel stroke with intention of thrombectomy was associated with lower degrees of disability, lower death rate, and higher rates of parenchymal hematoma both in thrombectomy-capable centers and in local stroke centers.

**Key Words:** acute stroke ■ emergency medical services ■ nonurban areas ■ thrombectomy ■ thrombolysis

The role of intravenous thrombolysis before endovascular thrombectomy for patients with a large-vessel occlusion stroke has been a matter of debate in the past years.[1] In 2015, after the pivotal trials demonstrated an overwhelming benefit of thrombectomy in patients with an anterior circulation large-vessel occlusion,[2] the question of whether thrombolytic treatment is still needed in candidates to receive thrombectomy became relevant. The benefit of thrombolysis-related reperfusion[3] and the potential synchronic effect of fibrinolytics during endovascular thrombectomy[4,5] might be hampered by a higher risk of hemorrhagic complications and delays in thrombectomy initiation. The majority of observational studies, although limited by subjective treatment selection bias, have shown a potential benefit of the combined therapy over endovascular thrombectomy alone.[6,7] However, recent randomized clinical trials have shown controversial results, with 2 trials that enrolled patients in Asia meeting prespecified noninferiority margins[8,9] of the thrombectomy alone approach and 4 trials showing trends toward better outcomes with the combined approach.[10–12]

Observational studies have included both directly admitted and transferred patients, although only patients who underwent endovascular thrombectomy were evaluated, a fact that might have introduced a selection bias. Randomized trials have evaluated the effect of intravenous thrombolysis among patients directly admitted to a thrombectomy-capable center, with limited applicability to patients in which thrombolytic treatment is administered at a local stroke center before transfer for thrombectomy evaluation.[13,14] Our goal is to evaluate whether the administration of thrombolytic treatment has varying effects on clinical and radiological outcomes in patients with large-vessel occlusion stroke, based on the type of stroke center where the treatment was given. Specifically, we will compare outcomes in patients who received thrombolytic treatment at a thrombectomy-capable center versus those who received treatment at a local stroke center before being transferred for thrombectomy evaluation in Catalonia, Spain.

## METHODS

### Data Sharing Statement

After publication, data will be available to any researcher who provides a methodologically sound study proposal that is approved by the central study team. Proposals can be submitted to the Division of Neurology at the Hospital Universitari Vall d'Hebron. Individual patients and hospitals will not be identifiable in any released data, and all appropriate information governance protocols will be followed.

### Standard Protocol Approvals, Registrations, and Patient Consent

This study was done under the Declaration of Helsinki and was approved by the Ethics Committee at Institut de Recerca Hospital Universitari Vall d'Hebron (Barcelona, Spain [code EOM(AG)035/2022(6019)]). Informed consent was waived to collect data though the Codi Ictus Catalunya registry because the data were anonymized and its aggregated data are publicly available online.

### Study Design and Population

The Catalonian stroke system of care was implemented in 2006 for the early recognition of patients with an acute stroke and for the rapid administration of thrombolytic treatment. In 2015, after endovascular thrombectomy was demonstrated to benefit patients with large-vessel occlusion, the network was adapted to increase the rate of thrombectomy among patients eligible for the treatment, in both urban and nonurban areas.[15] As of 2022, it provides acute stroke care through a network of 29 hospitals, including 7 thrombectomy-capable centers situated in Barcelona metropolitan area, covering ≈3.75 million inhabitants, and 22 local stroke centers situated outside metropolitan area, covering ≈3.85 million inhabitants, with a unique emergency medical services provider (Servei d'Emergències Mèdiques). During 2018 to 2019, 3 primary stroke centers started performing thrombectomy during working shifts; for the present analysis, we excluded patients treated with thrombectomy at these centers. Patients enrolled in the RACECAT (Direct Transfer to Endovascular Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory) trial[16] were included in this study.

All patients with a suspected acute stroke evaluated in the network are included in a prospective audited government-mandated registry, the Codi Ictus Catalunya, which links prehospital data provided by emergency medical services, data provided by local investigators at each stroke center and a blinded centralized evaluation of the modified Rankin Scale (mRS) at 90 days by certified evaluators. For this observational population-based study, we included patients who met the following inclusion criteria: (1) presence of a large-vessel occlusion on computed tomography (CT) angiography in the first hospital of attendance (including intracranial internal carotid artery, middle cerebral artery M1–M2, anterior cerebral artery A1–A2, posterior cerebral artery P1–P2, basilar artery, intracranial vertebral artery, and isolated extracranial internal carotid artery); (2) first image acquisition within 7 hours of stroke onset; (3) baseline National Institute of Health Stroke Scale of ≥5 at first hospital arrival, (4) baseline mRS of ≤2; and (5) intention to perform endovascular thrombectomy. This criterion differed according to the type of first center where patients were evaluated. Among patients initially evaluated at a thrombectomy-capable center, we included patients who underwent arterial puncture for endovascular thrombectomy. Among patients initially evaluated at a local stroke center, we included patients who were transferred from a local stroke center as thrombectomy candidates, regardless of whether they ultimately received thrombectomy treatment. Time of stroke onset was defined as last time seen well for patients with nonwitnessed onset time. All radiological and clinical variables, except for the degree of disability at 90 days, were reported by local investigators. Among patients treated with intravenous thrombolysis, we excluded from the analysis patients who were treated with tenecteplase (n=57 [1.2%]).

## Outcomes

The primary outcome of the study was the degree of disability at 90 days, as evaluated by the shift analysis on the mRS score, which was centrally evaluated by blinded certified investigators. Secondary outcomes included the following: (1) death rate at 90 days; (2) reperfusion before thrombectomy on first angiographic run (modified Thrombolysis in Cerebral Infarction of 2B–3, which represents a >50% of downstream reperfusion) or repeated CT angiography for transferred patients; (3) rate of successful reperfusion (modified Thrombolysis in Cerebral Infarction ≥2B) after endovascular thrombectomy, including patients who achieved reperfusion on first angiographic run or CT angiography; (4) rate of parenchymal hemorrhage type 1 or 2 on follow-up imaging on the basis of European Cooperative Acute Stroke Study criteria; (5) rate of symptomatic intracranial hemorrhage; and (6) time from first imaging acquisition to arterial puncture, if performed.

### Nonstandard Abbreviation and Acronym

| | |
|---|---|
| **acOR** | adjusted common odds ratio |
| **mRS** | modified Rankin Scale |
| **RACECAT** | Direct Transfer to Endovascular Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory |

### CLINICAL PERSPECTIVE

- Whether the efficacy of thrombolytic treatment has varying effects on clinical and radiological outcomes in patients with large-vessel occlusion stroke, based on the type of stroke center where the treatment was given, has been partially studied.
- Patients with acute ischemic stroke due to a large-vessel occlusion in Catalonia, Spain, who were treated with intravenous thrombolysis with the intention to undergo endovascular thrombectomy, had lower levels of disability and death at 90 days than those who were not treated with thrombolysis, both in thrombectomy-capable centers and in local stroke centers.
- Together with recent randomized trials that failed to demonstrate the noninferiority of withholding intravenous thrombolysis among patients treated with thrombectomy, these results reinforce the value of intravenous thrombolysis in acute stroke.

## Statistical Analysis

Descriptive analyses were used to define population baseline demographic, clinical, and imaging variables. Continuous variables are displayed as mean and SD or median and interquartile range (IQR; if not normally distributed). Categorical variables are displayed by number and frequencies. Baseline patient characteristics and clinical and radiological variables were compared between patients treated with or without intravenous thrombolysis according to the type of stroke center of first attendance (thrombectomy-capable center and local stroke center). To aid comparisons between groups, we calculated absolute standardized differences for continuous and categorical variables and considered standardized differences of ≥10% as a relevant imbalance between both groups. Based on a propensity-score approach, we applied inverse-probability-of-treatment weighting clustered at the type of stroke center to balance baseline characteristics between patients treated and not treated with intravenous thrombolysis across cohorts. The propensity weights were determined using a multivariable binary logistic model adjusted by variables at first hospital arrival (Table 1). We managed the potential bias induced by extreme weights trimming weights that exceeded the first (lower boundary) and 99th (upper boundary) percentile of weights.[17] Missing data on propensity score model covariates, the primary outcome (missing in 165 patients [10%] treated with thrombolysis, and 172 patients [10%] not treated with thrombolysis) and secondary outcomes were handled with the use of multiple imputation with 5 iterations using all variables included in the propensity score model and the outcomes.

A doubly robust estimator based on the inverse-probability-of-treatment weighting and an ordinal or a binary logistic regression–based approach, depending on the outcome variable, was used to estimate the effect of intravenous thrombolysis on the outcomes. The logistic regression adjustment was done with the following variables: age, sex, time of day, unwitnessed stroke, time from onset to first image acquisition, National Institute of Health Stroke Scale score, Alberta Stroke Program Early CT Score, occlusion location, presence of a tandem occlusion, and anticoagulation intake. Robust estimates of standard errors were used to account for within-subject correlation due to weighting. The heterogeneity of the effect across types of centers (thrombectomy-capable center and local stroke center) on the outcomes was tested with a multiplicative interaction term between thrombolytic treatment and type of center. We report a sensitivity analysis including only patients with an occlusion involving the intracranial internal carotid artery or middle cerebral artery (M1–M2). We also report the mean difference and 95% CIs of the time from image acquisition to arterial puncture to evaluate whether treatment with thrombolysis could delay thrombectomy initiation. To assess whether time from onset to thrombolysis administration and time from thrombolysis administration to thrombectomy initiation modified the treatment effect on the overall cohort, we used time of first image acquisition as a surrogate time point for thrombolysis administration and added an interaction term between the time interval of interest and thrombolysis treatment.

For all analyses, patients not treated with thrombolysis were considered as the reference category. All reported *P* values are 2-sided and have not been adjusted for multiple testing. All significance thresholds were set at 2-sided $P<0.05$. Statistical analyses were performed with R version 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

# RESULTS

The analysis included 2268 patients directly admitted to a thrombectomy-capable center, of whom 1270 (56%) were treated with thrombolysis, and 938 patients transferred from a local stroke center, of whom 601 (64%) were treated with thrombolysis, between January 2017 and December 2021 (Figure 1). Overall, median age was 74 (IQR, 64–82), 1521 patients (47%) were women, median National Institute of Health Stroke Scale score was 17 (IQR, 12–21), median time from stroke onset to first image acquisition was 100 minutes (IQR, 66–167), and 2761 patients (86%) had an intracranial occlusion involving the internal carotid artery or the middle cerebral artery. Among patients transferred from a local stroke center, 616 patients (66%) were treated with endovascular thrombectomy, with no difference between patients treated with thrombolysis (394/601 [66%]) or not treated with thrombolysis (222/337 [66%]). Reasons why patients were not treated with thrombolysis or, for patients transferred from local stroke centers, thrombectomy are shown in Tables S1 and S2.

As compared with patients not treated with thrombolysis, patients treated with thrombolysis were younger (median, 73 [IQR 63–81] years versus 75 [IQR, 65–82] years), had lower baseline mRS score (mean, 0.39 [SD ±0.68] versus 0.58 [SD ±0.76]), shorter time from onset to image acquisition (median, 93 [IQR, 66–137] versus 107 [65–225]), higher baseline Alberta Stroke Program Early Computed Tomography Score (mean, 9.2 [SD ±1.3] versus 8.9 [SD ±1.5]) and lower rates of unwitnessed stroke onset

**Table 1. Baseline Characteristics of All Included Patients According to Thrombolysis Treatment Administration**

| | Not treated with intravenous thrombolysis (N=1607) | Treated with intravenous thrombolysis (N=1599) | Standardized difference |
|---|---|---|---|
| Male sex, n (%) | 832 (52) | 853 (53) | 0.01 |
| Age, y, mean (SD) | 72 (13) | 71 (13) | 0.12 |
| Time from stroke onset to first imaging, min, mean (SD) | 148 (110) | 110 (63) | 0.42 |
| First hospital arrival during nighttime, n (%) | 538 (33) | 423 (26) | 0.07 |
| Comorbidities, n (%) | | | |
| Hypertension | 913 (62) | 867 (58) | 0.04 |
| Dyslipidemia | 623 (42) | 604 (40) | 0.02 |
| Diabetes | 305 (21) | 279 (19) | 0.02 |
| Smoking | 188 (13) | 252 (17) | 0.04 |
| Alcohol intake | 69 (5) | 86 (6) | 0.01 |
| Atrial fibrillation | 537 (36) | 199 (13) | 0.23 |
| Coronary heart disease | 211 (14) | 161 (11) | 0.04 |
| Anticoagulation intake | 423 (29) | 67 (5) | 0.24 |
| Missing data | 132 (8) | 103 (6) | |
| Prestroke modified Rankin Scale,[4] n (%) | | | |
| 0 | 949 (59) | 1150 (72) | 0.12 |
| 1 | 386 (24) | 270 (17) | 0.07 |
| 2 | 272 (17) | 179 (11) | 0.06 |
| NIHSS score, mean (SD) | 16.9 (6.7) | 16.4 (6.2) | 0.07 |
| Unknown time from onset, n (%) | 433 (27) | 167 (10) | 0.16 |
| ASPECTS score, mean (SD) | 8.9 (1.5) | 9.2 (1.3) | 0.18 |
| Missing data* | 300 (19) | 195 (12) | |
| Vessel occlusion on vascular imaging, n (%) | | | |
| Intracranial internal carotid artery | 230 (14) | 208 (13) | 0.01 |
| Middle cerebral artery (M1) | 777 (48) | 912 (57) | 0.08 |
| Middle cerebral artery (M2) | 331 (21) | 303 (19) | 0.02 |
| Anterior cerebral artery | 15 (1) | 13 (1) | 0.01 |
| Posterior cerebral artery | 52 (4) | 42 (3) | 0.01 |
| Basilar artery | 111 (7) | 78 (5) | 0.02 |
| Vertebral artery | 9 (1) | 3 (1) | 0.01 |
| Extracranial internal carotid artery | 82 (5) | 40 (3) | 0.03 |
| Tandem occlusion, n (%) | 184 (11) | 214 (13) | 0.02 |

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Scale; and NIHSS, National Institute of Health Stroke Scale.
*Patients with an ischemic stroke involving the anterior cerebral artery or posterior circulation arteries were considered as missing (n=445).



(167/1599 [10%] versus 433/1607 [27%]), atrial fibrillation diagnosis (199/1599 [12%] versus 537/1607 [33%]), and anticoagulation intake (67/1599 [5%] versus 423/1607 [29%]) (Table 1**)**. After adjustment for inverse probability of treatment weighting, all covariates were well balanced between patients treated and not treated with intravenous thrombolysis across both types of stroke centers (ie, mean standardized mean differences across imputed data sets were <0.1, Figures S1, S2).

## Primary Outcome

On the primary outcome analysis, patients treated with thrombolysis had lower degrees of disability at 90 days than patients not treated with thrombolysis (median mRS [IQR], 3 [1–4] versus 4 [2–6], adjusted common odds ratio [acOR] for a better outcome 1.47, [95% CI, 1.25–1.73]). The average effect of intravenous thrombolysis administration on the primary outcome did not differ between patients directly admitted to a thrombectomy-capable center (acOR 1.50, 95% CI 1.24–1.81) and patients transferred from a local stroke center (acOR, 1.44 [95% CI, 1.04–2.01]; $P_{interaction}$=0.68; Figure 2). The sensitivity analysis performed restricted to patients with an anterior circulation intracranial large-vessel occlusion showed similar results, with an acOR of 1.52 (95% CI, 1.24–1.86) for patients directly admitted to a thrombectomy-capable center and an acOR of 1.41 (95% CI, 1.02–1.91) for patients transferred from a local stroke center ($P_{interaction}$= 0.45).

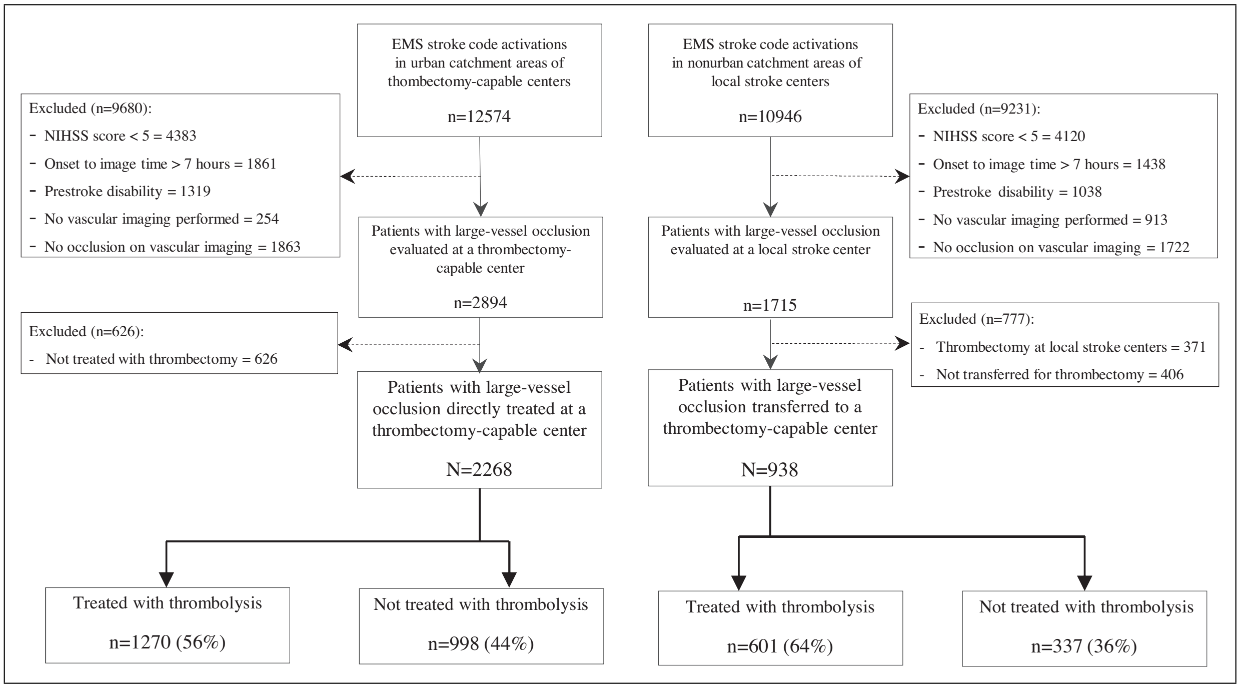


**Figure 1. Flowchart of all included patients from the Codi ictus Catalunya registry**. EMS indicates emergency medical services; and NIHSS, National Institute of Health Stroke Scale.

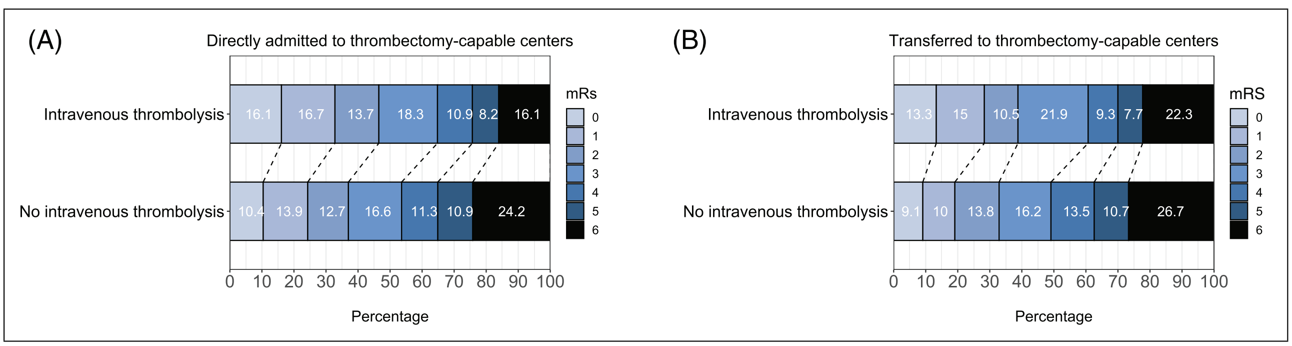


**Figure 2. Effect of intravenous thrombolysis on 90-days mRS according to type of center**. Stacked barplots representing the degree of disability at 90 days in patients with large-vessel occlusion directly admitted to thrombectomy-capable centers (**A**) and patients transferred from local stroke centers (**B**) according to intravenous thrombolysis administration. mRS indicates modified Rankin Scale.

## Secondary Outcomes

As compared with patients not treated with thrombolysis, patients treated with thrombolysis had similar odds of successful reperfusion (1356/1667 [81%] versus 1918/2421 [79%]; aOR, 1.20 [95% CI, 0.95–1.51]), higher rates of parenchymal hematoma (75/1599 [5%] versus 52/1607 [3%]; aOR, 1.72 [95% CI, 1.06–2.79]), comparable rates of symptomatic intracranial hemorrhage (63/1667 [4%] versus 76/2421 [3%]; aOR, 1.39 [95% CI, 0.85–2.26]), and lower death rate at 90 days (270/1599 [17%] versus 422/1607 [26%]; aOR, 0.65 [95% CI, 0.51–0.83]). The observed average effect of intravenous thrombolysis on these secondary outcomes was comparable between patients directly admitted to a thrombectomy-capable center and patients transferred from a local stroke center (Table 2).

Sixty-eight (3%) patients directly admitted to a thrombectomy-capable center (46/998 [5%] treated with thrombolysis and 22/1270 [2%] not treated with thrombolysis; aOR, 1.81 [95% CI, 1.02–3.23]) had no evidence of occlusion amenable for thrombectomy on first angiographic run, as compared with 137 (15%) patients transferred from a local stroke center (103/601 [17%] treated with thrombolysis and 24/337 [7%] not treated with thrombolysis; aOR, 4.10 [95% CI, 2.35–7.15]) with no evidence of occlusion amenable for thrombectomy on repeated vascular imaging or first angiographic run at the thrombectomy-capable center ($P_{interaction}$=0.06).

**Table 2. Primary and Secondary Outcomes Overall Effect and Subgroup-Specific Effects**

| | Not treated with thrombolysis (N=1607) | Treated with thrombolysis (N=1599) | Effect variable | Overall effect (95% CI) | Subgroup | Subgroup effect (95% CI) | $P_{interaction}$ |
|---|---|---|---|---|---|---|---|
| Shift analysis on the mRS at 90 d, median (IQR) | 4 (2–6) | 3 (1–4) | Common odds ratio | 1.47 (1.25–1.73) | Thrombectomy-capable center | 1.50 (1.24 to 1.81) | 0.68 |
| | | | | | Local stroke center | 1.44 (1.04–2.01) | |
| Mortality rate at 90 d, n (%) | 352 (22) | 239 (15) | Odds ratio | 0.65 (0.51–0.83) | Thrombectomy-capable center | 0.76 (0.46–1.26) | 0.38 |
| | | | | | Local stroke center | 0.61 (0.46–0.79) | |
| Parenchymal hemorrhage, n (%) | 52 (3) | 75 (5) | Odds ratio | 1.72 (1.06–2.79) | Thrombectomy-capable center | 1.48 (0.83 to 2.65) | 0.52 |
| | | | | | Local stroke center | 1.96 (0.86 to 4.45) | |
| Symptomatic intracranial hemorrhage, n (%) | 76 (3) | 63 (4) | Odds ratio | 1.39 (0.85–2.26) | Thrombectomy-capable center | 1.32 (0.72 to 2.44) | 0.75 |
| | | | | | Local stroke center | 1.40 (0.61 to 3.2) | |
| Reperfusion before thrombectomy, n (%) | 46 (3) | 149 (9) | Odds ratio | 2.82 (1.72–4.12) | Thrombectomy-capable center | 1.81 (1.02 to 3.23) | 0.06 |
| | | | | | Local stroke center | 4.10 (2.35 to 7.15) | |
| Successful reperfusion overall, n (%) | 1296 (80) | 1310 (82) | Odds ratio | 1.20 (0.95–1.51) | Thrombectomy-capable center | 1.17 (0.87 to 1.59) | 0.71 |
| | | | | | Local stroke center | 1.16 (0.77 to 1.72) | |
| Time from image acquisition to groin puncture, mean (SD) | 79 (65) | 94 (66) | Mean difference | 15 (10–20) | Thrombectomy-capable center | 10 (−4 to 24) | 0.42 |
| | | | | | Local stroke center | 18 (−2 to 38) | |

Effects were estimated with a doubly robust estimator based on an inverse-probability of treatment weighting approach and a logistic-regression adjustment. Mean difference in time from image acquisition to groin puncture are crude (without adjustment). IQR indicates interquartile range; and mRS, modified Rankin Scale.

Time from image acquisition to arterial puncture was delayed (mean difference, 15 minutes [95% CI, 10–20]) in patients treated with thrombolysis (mean, 94 [SD ±66 minutes]), as compared with patients not treated with thrombolysis (mean, 79 [SD ±64 minutes]). The time analysis that evaluated the potential effect modification of time from onset to image acquisition or from image acquisition to groin puncture showed that the effect of intravenous thrombolysis on the primary outcome was stronger with shorter time from image acquisition to thrombectomy initiation ($P_{interaction}$=0.03), with no effect modification of time from onset to image acquisition ($P_{interaction}$=0.15).

## DISCUSSION

In this population-based observational study, we found that patients with acute ischemic stroke due to a large-vessel occlusion who were treated with intravenous thrombolysis with the intention to undergo endovascular thrombectomy had lower levels of disability and death at 90 days than those who were not treated with thrombolysis. The analysis included all patients transferred from local stroke centers as thrombectomy candidates independently of whether endovascular thrombectomy was finally performed, considering the potential benefit of reperfusion before arrival to the thrombectomy-capable center[18] on the treatment effect estimations. The observed average treatment effect of intravenous thrombolysis was independent of the type of stroke center in which thrombolysis was administered. Our results support the efficacy and safety of the drip-and-ship approach among patients with a large-vessel stroke eligible for intravenous thrombolysis that are initially evaluated at a local stroke center and are subsequently transferred as thrombectomy candidates.

We observed higher rates of parenchymal hemorrhage after treatment, although the rate of symptomatic intracranial hemorrhage did not differ, and time delay in thrombectomy initiation among patients treated with thrombolysis (mean difference, 15 minutes). However, these negative effects were limited and compensated considering the overall beneficial effect of thrombolysis on clinical outcomes. Reperfusion before thrombectomy was more frequent among patients treated with thrombolysis, with a larger absolute difference among patients in which thrombolysis was administered at a local stroke center. Data from previous studies have shown that thrombolysis-related reperfusion was more prevalent among patients with a longer elapsed time between thrombolysis administration and repeated vascular imaging.[18,19] Moreover, in patients with large-vessel occlusion, reperfusion before thrombectomy has been associated with higher rates of good functional outcome.[18,20] We observed a heterogeneity in the treatment effect of intravenous thrombolysis according to the elapsed time between image acquisition, a time point that was used as a subrogate of thrombolysis administration, and thrombectomy initiation. A multicenter study showed that delay in the time between thrombolysis administration and thrombectomy initiation was associated with a worse functional prognosis, worse reperfusion rates after thrombectomy and a higher risk of hemorrhagic transformation.[4] Interventions that aim to reduce time from thrombolysis administration and thrombectomy initiation, including direct transfer to angiography suite protocols,[21] interventions in local stroke centers to reduce interhospital transfer times[22] and the implementation of mobile stroke units,[23] or even an additional administration of thrombolytics during endovascular thrombectomy,[5] should be evaluated. There was no evidence of a treatment effect modification according to the time from stroke onset to thrombolysis administration, which is considered one the most powerful predictors of thrombolysis efficacy.[24] A lack of statistical power to detect a smaller difference and the fact that endovascular thrombectomy might have confounded the effect of time to thrombolysis on the primary outcome could be potential explanations. Data from randomized trials did not show an effect modification of any time interval on outcomes,[8–10,25] although individual patient-level meta-analysis is needed to mitigate the lack of statistical power in subgroup analyses of individual trials and to assess in which conditions the effect of intravenous thrombolysis is stronger.[26]

The study was performed within a stroke system of care with largely protocolized practice patterns, a unique emergency medical services provider, little variations in outcomes between centers, and consistent workflow and treatment times.[16] Outcomes in patients directly admitted or transferred to a thrombectomy-capable center might differ in regions with larger differences in time from stroke onset to endovascular thrombectomy initiation. Nonetheless, our results emphasize that withholding thrombolysis could lead to the denial of any reperfusion treatment more frequently in patients with large-vessel occlusion transferred from local stroke centers due to time delays until the indication of endovascular thrombectomy at the thrombectomy-capable center is evaluated.

The main strengths of our study are that it encompassed most of the eligible study population with a large-vessel occlusion of a confined area with respect to health care access through 6 years and that the primary outcome was centrally evaluated by blinded investigators to limit the degree of evaluation bias. The main limitations of the study are that the treatment decisions were not randomized, a fact that might have introduced a treatment selection bias, and that the treatment effect estimation might differ in other stroke systems of care with varying practice patterns and time delays in reperfusion treatment administration. We based the analysis on an inverse-probability-of-treatment-weighting approach, which mitigates the potential bias due to treatment indication, although the presence of unmeasured or unknown confounders cannot be discarded, and results should be taken with caution. Other limitations are the exclusion of patients treated with tenecteplase, a thrombolytic agent that has been proven to induce higher rates of thrombolysis-related reperfusion[27] and is logistically easier to administer since it does not require a continuous infusion pump, that secondary outcomes were reported by local investigators, and that patients in whom vascular imaging was not performed at the local stroke center were excluded from this analysis, a fact that might have introduced a selection bias.

## CONCLUSION

Among patients with a large-vessel occlusion stroke with the intention to perform endovascular thrombectomy, administration of intravenous thrombolysis was consistently associated with lower degrees of disability at 90 days, lower death rate, and higher rate of parenchymal hemorrhage both in thrombectomy capable centers and in local stroke centers. Together with recent randomized trials that failed to demonstrate the noninferiority of withholding intravenous thrombolysis among patients treated with thrombectomy, these results reinforce the value of intravenous thrombolysis in acute stroke. Thrombolysis-related reperfusion and a potential synchronic effect of thrombolytics during endovascular thrombectomy might explain the observed benefit of thrombolysis.

## ARTICLE INFORMATION

Received November 10, 2022; Accepted April 3, 2023

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## Acknowledgments

None.

## Sources of Funding

None.

## Disclosures

Natalia Perez de la Ossa: grant from the Spanish Ministry of Health co financed by Fondo Europeo de Desarrollo Regional (Instituto de Salud Carlos III, Red Temática de Investigación Cooperativa RETICS-INVICTUS-PLUS RD0016/0019/0020), and from the PERIS programme from the Catalan Health Government (project SLT008/18/0007). Antoni Davalos reports consultancy and advisory board fees from Medtronic Neurovascular (Steering Committee STAR). Carlos Molina has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers-Squibb, Covidien, Cerevast, and Brainsgate. Marc Ribó is advisor and shareholder in Anaconda Biomed and Methinks and received grants and personal fees from Medtronic, personal fees from Stryker, Cerenovus, Philips, and Apta Targets. Other authors have nothing to disclose.

## Supplemental Materials

Supplementary information

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