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Adjunctive Intra-Arterial Alteplase After Successful Thrombectomy for Acute Ischemic Stroke
The CHOICE-2 Randomized Clinical Trial

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IMPORTANCE Despite high recanalization rates with endovascular thrombectomy for acute ischemic stroke due to large vessel occlusion, functional outcomes remain suboptimal. The benefit of adjunctive intra-arterial thrombolysis after successful thrombectomy is uncertain.

OBJECTIVE To assess whether adjunctive intra-arterial alteplase after successful thrombectomy improves functional outcomes and cerebral reperfusion.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label trial with blinded outcome assessment conducted at 14 stroke centers in Spain from December 11, 2023, through November 26, 2025. A total of 440 patients with acute ischemic stroke due to large vessel occlusion treated with thrombectomy within 24 hours and achieving an expanded Treatment in Cerebral Ischemia score of 2b50 to 3 were randomized.

INTERVENTIONS Thrombectomy plus intra-arterial alteplase (0.225 mg/kg; maximum dose, 20 mg/kg) infused over 15 minutes (n = 221) or thrombectomy alone (n = 219).

MAIN OUTCOMES AND MEASURES The primary outcome was an excellent functional outcome at 90 days, which was defined as a modified Rankin Scale score of 0 or 1. There were 6 secondary outcomes, including residual hypoperfusion on follow-up computed tomography perfusion. The safety outcomes included symptomatic intracranial hemorrhage and death.

RESULTS Of 3786 patients treated with thrombectomy, 2776 (73%) fulfilled angiographic criteria and 440 (12%) were randomized. There were 433 patients who were treated as randomized (median age, 76 [IQR, 75-78] years; 51% female). At 90 days, 57.5% of patients (123/214) in the thrombectomy plus intra-arterial alteplase group had a modified Rankin Scale score of 0 or 1 vs 42.5% of patients (93/219) in the thrombectomy alone group (adjusted risk difference, 15.0% [95% CI, 5.7% to 24.3%]; $P = .002$). Of 6 secondary outcomes, 4 showed no significant between-group differences. Residual hypoperfusion occurred in 28.6% (55/192) of patients in the thrombectomy plus intra-arterial alteplase group vs 50.5% (96/190) of patients in the thrombectomy alone group (adjusted risk difference, −22.0% [95% CI, −31.5% to −12.4%]; $P < .001$) and symptomatic intracranial hemorrhage occurred in 1.4% (3/214) vs 0.5% (1/219), respectively (adjusted odds ratio, 3.10 [95% CI, 0.32 to 30.0]; $P = .33$). Mortality at 90 days was 12.1% (26/214) in the thrombectomy plus intra-arterial alteplase group vs 6.4% (14/219) in the thrombectomy alone group (adjusted risk difference, 5.9% [95% CI, 0.5% to 11.3%]; $P = .03$).

CONCLUSIONS AND RELEVANCE Among patients with acute ischemic stroke and successful thrombectomy, adjunctive intra-arterial alteplase increased the proportion achieving excellent functional outcome at 90 days without a significant increase in symptomatic intracranial hemorrhage. Higher mortality in the thrombectomy plus intra-arterial alteplase group warrants further study.

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Supplemental content

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Endovascular thrombectomy is the standard of care for acute ischemic stroke due to large vessel occlusion and has high rates of arterial recanalization.[1] However, despite frequent angiographic success, fewer than half of treated patients obtain functional independence (a modified Rankin Scale [mRS] score of 0, 1, or 2), and only about one-third attain an excellent outcome (an mRS score of 0 or 1).[2] Although these findings have largely been attributed to irreversible tissue injury incurred before reperfusion, it is also possible that macrovascular recanalization does not fully reflect the adequacy of tissue-level reperfusion, which is a factor that may be critical to neurological recovery.

Microvascular hypoperfusion after successful recanalization, often referred to as the *no-reflow phenomenon*,[3-5] has been described in pathological and imaging studies, but its clinical significance and therapeutic implications remain uncertain. Preliminary evidence suggested that low-dose intra-arterial alteplase administered after successful thrombectomy may enhance tissue-level reperfusion and improve functional outcomes without increasing major safety events.[6] Subsequent studies conducted in China have yielded mixed results,[7-10] underscoring the need for definitive evidence from a randomized clinical trial.

The Chemical Optimization of Cerebral Embolectomy 2 (CHOICE-2) trial was designed to confirm the findings of the CHOICE trial[6] and determine whether adjunctive intra-arterial alteplase administered immediately after successful thrombectomy improves 90-day functional outcome and cerebral perfusion in patients with anterior circulation large vessel occlusion.

Key Points

Question Among patients with acute ischemic stroke due to large vessel occlusion who had successful recanalization after endovascular thrombectomy, does adjunctive intra-arterial alteplase improve functional outcomes compared with thrombectomy alone?

Findings In this randomized, open-label, multicenter clinical trial including 440 patients, adjunctive intra-arterial alteplase after successful thrombectomy resulted in a higher proportion of patients achieving excellent functional outcome (modified Rankin Scale score of 0 or 1) at 90 days compared with thrombectomy alone (57.5% vs 42.5%), a statistically significant difference.

Meaning Adjunctive intra-arterial alteplase after successful thrombectomy may improve functional recovery in patients with large vessel occlusion stroke.

Methods

Trial Design and Oversight

This was an investigator-initiated, multicenter, open-label, phase 3 randomized clinical trial with blinded assessment of clinical and imaging outcomes. The trial evaluated adjunctive intra-arterial alteplase administered immediately after successful endovascular thrombectomy for anterior circulation acute ischemic stroke. Fourteen tertiary stroke centers in Spain participated. A detailed description of the trial protocol was published[11] and appears in Supplement 1. The statistical analysis plan appears in Supplement 2. The trial imaging framework appears in Supplement 3.

The trial protocol was reviewed and approved by an independent institutional review board and the trial was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.[12] All patients or their legally authorized representatives provided written or oral informed consent, in most instances during performance of the endovascular procedure. This trial report was prepared in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The lists of the trial organization, sites, and investigators appear in the eLists in Supplement 4.

An independent data and safety monitoring board oversaw participant safety and reviewed accumulating data at prespecified intervals. An independent blinded imaging core laboratory adjudicated all follow-up imaging measurements, including perfusion deficits and the infarct expansion ratio. Trial operations and pharmacovigilance support were provided by an independent contract research organization. Additional information about the imaging core laboratory appears in the eMethods in Supplement 4.

Participants

Eligible adults (≥18 years of age) presented with acute ischemic stroke due to isolated occlusion of the internal carotid, middle cerebral (M1 or proximal M2), or anterior cerebral artery. Patients were required to have no substantial prestroke disability (an mRS score ≤1) and to undergo endovascular thrombectomy and have at least 50% reperfusion, corresponding to a modified Thrombolysis in Cerebral Infarction (TICI) score of 2b50 to 3 on cerebral angiography as assessed by local investigators.

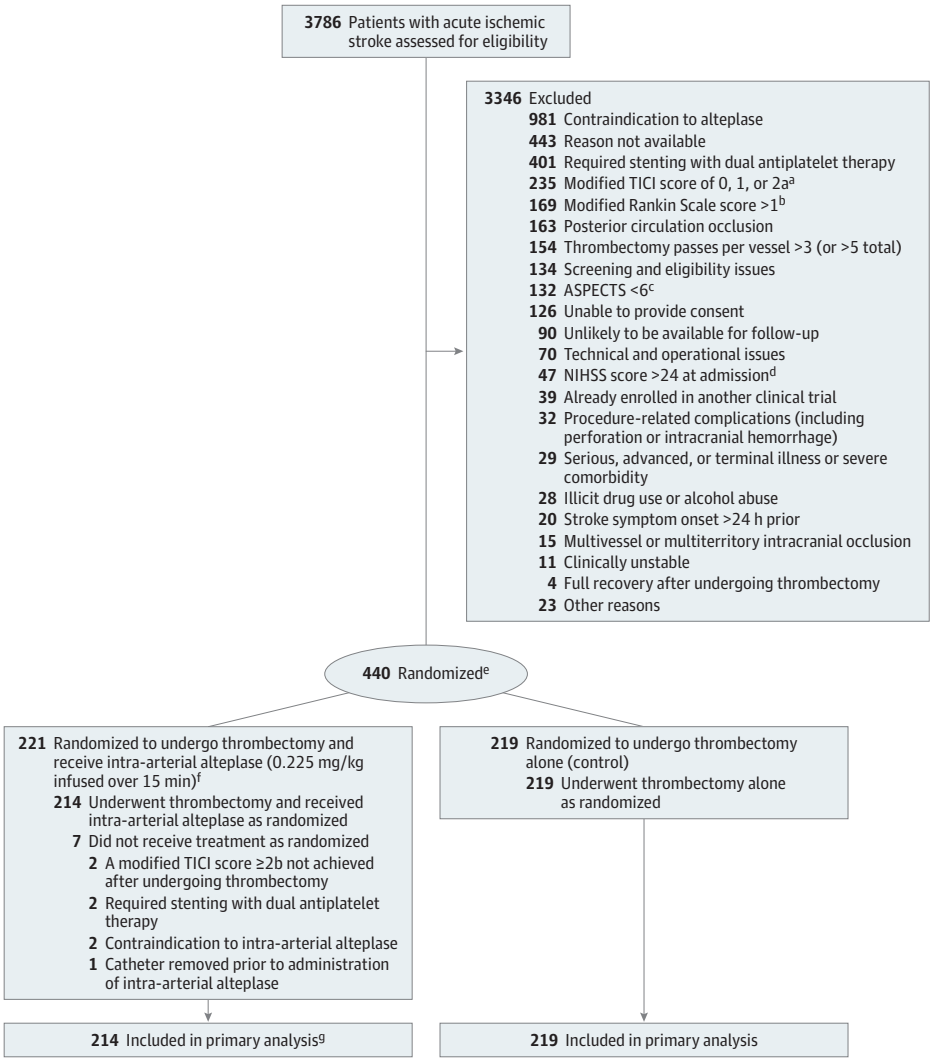
Patients could be enrolled within 4.5 hours of last known well if they had an Alberta Stroke Program Early CT (computed tomography [CT]) Score (ASPECTS) of 6 or higher on noncontrast CT (ASPECTS range, 0-10; 1 point is subtracted for any evidence of early ischemic change in each defined region on the CT scan), or within 24 hours if advanced imaging demonstrated salvageable ischemic tissue according to institutional protocols.

Exclusion criteria included contraindications to intravenous thrombolysis, known coagulopathy, intracranial hemorrhage, stenting requiring dual antiplatelet therapy, large established infarction on baseline imaging, and an admission National Institutes of Health Stroke Scale (NIHSS) score greater than 25. Complete eligibility criteria appear in eTable 1 in Supplement 4 and in the trial protocol in Supplement 1.

Randomization and Blinding

After confirmation of successful reperfusion and eligibility, patients were randomly assigned in a 1:1 ratio to undergo thrombectomy plus intra-arterial alteplase or thrombectomy alone (**Figure 1**). Randomization was performed through a secure

Figure 1. Diagram Depicting Flow of Patients Through the Trial



[a]TICI indicates Thrombolysis in Cerebral Infarction (range, 0-3; higher scores indicate greater reperfusion).

[b]The score range is 0 to 6 (higher scores indicate greater disability).

[c]ASPECTS indicates Alberta Stroke Program Early CT (computed tomography) Score (range, 0-10; lower scores indicate more extensive ischemic changes).

[d]NIHSS indicates National Institutes of Health Stroke Scale (range, 0-42; higher scores indicate greater neurological deficit).

[e]Patients were randomized while undergoing thrombectomy after eligibility was confirmed (including requirement of an expanded TICI score of 2b50 to 3).

[f]The maximum dose was 20 mg/kg.

[g]Seven patients were excluded because the study treatment was not initiated for the following reasons: misunderstanding of the treatment assignment (1 patient), international normalized ratio greater than 1.7 detected after randomization (1 patient), acute stenting requiring dual antiplatelet therapy (2 patients), intracranial hemorrhage identified after randomization (1 patient), and inadequate angiographic score detected after randomization (2 patients).

web-based system using permuted block sizes that were multiples of 2 stratified according to center and prior intravenous thrombolysis (yes or no). Treating clinicians were aware of group assignments, but all outcome assessors, core laboratory readers, and statisticians remained blinded throughout the trial.

Interventions

All thrombectomy procedures were performed according to the standard practices at the participating centers using stent retrievers, aspiration catheters, or combined techniques at the discretion of the operator. To maintain procedural comparability, the protocol limited thrombectomy to a maximum of 3 passes per vessel or 5 passes per patient.

Patients assigned to the intervention group underwent thrombectomy and received adjunctive intra-arterial alteplase at a dose of 0.225 mg/kg of body weight (maximum dose, 20 mg/kg). Intra-arterial alteplase was continuously infused over 15 minutes via a microcatheter positioned in the terminal internal carotid artery ipsilateral to the ischemic territory, immediately after confirmation of clinical and angiographic eligibility. Patients assigned to the control group underwent thrombectomy alone and did not receive adjunctive therapy.

After treatment, all patients were admitted to a stroke unit or intensive care unit and managed in accordance with European and US guideline-based standards, including blood pressure management, monitoring for neurological deterioration, and secondary prevention measures.[1,13]

Imaging

Baseline neuroimaging at all sites included cerebral angiography, noncontrast CT, and CT angiography; additional perfusion imaging was performed according to site-specific protocols. Follow-up imaging was obtained at 36 hours (± 24 hours) after randomization and included CT perfusion, noncontrast CT, and CT angiography as clinically indicated. All imaging data were uploaded to a central core laboratory. The imaging readers

were blinded to treatment allocation. Clinical outcomes were evaluated via cerebral angiograms using the expanded TICI score and perfusion deficits were assessed using predefined definitions, quantitative thresholds, and standardized volumetric workflows.

Infarct expansion ratio was calculated as the ratio of follow-up infarct volume to baseline ischemic tissue volume that was derived from noncontrast CT data or CT perfusion maps when available. Residual hypoperfusion was defined on CT perfusion as regions of delayed perfusion (>3 seconds) with a minimum cluster size of 10 contiguous voxels. In patients achieving an expanded TICI score of 3, hypoperfusion was further classified as microvascular hypoperfusion (eMethods in Supplement 4).

Outcomes

Patient demographic characteristics, medical history, laboratory values, imaging findings, stroke symptoms, and neurological severity were assessed at presentation (eTable 2 in Supplement 4). The primary outcome was an excellent functional outcome at 90 days, which was defined as an mRS score of 0 or 1. The mRS has a score range from 0 (no disability) to 6 (death). The mRS scores were obtained through structured telephone and video interviews conducted by certified central assessors who were unaware of trial group assignments. Interviews were performed during outpatient visits at the study sites.

The primary outcome was originally defined as the proportion of hypoperfusion on CT perfusion imaging. During month 12 of the study, and without a prespecified interim analysis, the primary outcome was modified. The trial had initially been designed as giving priority to an objective neuroimaging mechanistic end point given its open-label design. The change to an mRS score of 0 or 1 was made to enhance clinical relevance, interpretability, and comparability of the results based on emerging randomized evidence in the field and recognizing the general acceptance of blinded observer ratings when using the mRS.

The secondary outcomes included residual hypoperfusion on follow-up CT perfusion (yes vs no), the volume of residual hypoperfusion, and the infarct expansion ratio. The infarct expansion ratio was assessed by comparing baseline noncontrast CT and follow-up noncontrast CT performed at 36 hours (± 24 hours). Other clinical secondary outcomes assessed at 90 days included the Barthel Index (range, 0-100; higher scores indicate greater independence in activities of daily living; scores of 95-100 indicate functional independence) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) score (a patient-reported measure of health-related quality of life; higher scores indicate better health status). Functional outcome was also evaluated with an ordinal (shift) analysis of mRS scores, in which a score of 5 (severe disability) or 6 (death) were combined into a single worst outcome category.

Safety outcomes included symptomatic intracranial hemorrhage at 36 hours (± 24 hours) according to European Cooperative Acute Stroke Study III criteria (neurological deterioration of ≥4 points on the NIHSS score in association with intracranial hemorrhage as a predominant cause as determined by site investigators),[14] any intracranial hemorrhage, serious adverse events, and all-cause mortality at 90 days.

Sample Size Calculation

Based on the results from the CHOICE trial,[6] the study was powered to detect an absolute difference of 14 percentage points in the proportion of patients with an mRS score of 0 or 1 at 90 days, assuming a control event rate of 40% and a 2-sided type I error of 5%. A total enrollment of 440 patients (220 per group) was planned, accounting for a dropout rate of 5%. This sample size also provided at least 95% power to detect an absolute difference of 18 percentage points in the presence of residual hypoperfusion, assuming a control group rate of 58%.[7]

Statistical Analysis

A detailed description of the analytic approach is provided in the statistical analysis plan (Supplement 2). The primary efficacy analysis was performed in the modified full analysis set, which was defined as all randomized patients who initiated the assigned study treatment; this population was identical to the safety population. The per-protocol population included patients without major protocol deviations. An exploratory full analysis set, including all randomized patients regardless of treatment received, was used for the sensitivity analyses.

The primary outcome analysis estimated the adjusted risk difference for the primary outcome using a binomial regression model with an identity link, adjusting for prior intravenous thrombolysis. The sensitivity analyses included log binomial models to estimate relative risks, models incorporating additional baseline covariates, and models including treating center as a random effect. The sensitivity analyses included assessments of the entire as-randomized population, the as-treated population, and the treated per-protocol population. Prespecified subgroup analyses examined effect modification according to age, sex, pretreatment intravenous thrombolysis, expanded TICI score, time to reperfusion, and baseline glucose level.

A shift analysis of mRS scores at 90 days was performed using a proportional odds model. The proportional odds assumption was assessed using the score test for proportional odds. A prespecified stratified nonparametric van Elteren test was performed as a sensitivity analysis. The volume of hypoperfusion and the infarct expansion ratio were analyzed using generalized linear mixed models with a γ distribution and log link. Because follow-up CT perfusion was performed within a prespecified window of 36 hours (± 24 hours) after randomization, the post hoc sensitivity analyses were conducted to account for potential time-dependent effects.

For the binary outcome of residual hypoperfusion, the binomial regression model was additionally adjusted for time from randomization to CT perfusion acquisition (continuous variable). An additional model including a treatment assignment × time to imaging interaction term was used to evaluate potential effect modification. Post hoc

analyses examined the association between residual hypoperfusion and unfavorable functional outcome (mRS scores of 2 to 6), as well as treatment effects restricted to patients with complete reperfusion (expanded TICI score of 3) as assessed by the central core laboratory. The safety outcomes were analyzed using the same methods as those applied to the primary outcome. Missing 90-day mRS scores were handled using a prespecified hierarchical approach detailed in the statistical analysis plan (Supplement 2) and briefly as follows: central blinded assessment, then local assessment, then assignment of an mRS score of 4 for patients known to be alive at 90 days (± 14 days).

As a sensitivity analysis, missing mRS scores were imputed using multiple imputation by fully conditional specification. The imputation model included age, sex, prior receipt of intravenous alteplase, randomized treatment assignment, study site, time from symptom onset to randomization, and prestroke mRS score. A total of 100 imputed datasets were generated, and treatment effect estimates were combined using Rubin rules. Neuroimaging outcomes were initially analyzed without formal imputation (as prespecified in the statistical analysis plan in Supplement 2). We additionally performed sensitivity analyses using multiple imputation (eTable 3 in Supplement 4). The Barthel Index analyses were conducted in the modified full analysis set.

All secondary analyses were exploratory. Two-sided *P* values are reported without adjustment for multiplicity. All statistical tests were 2-sided and a significance threshold of $P < .05$ was used. The analyses were performed using SAS version 9.4M7 (TS1M7) (SAS Institute Inc).

Results

Patients

From December 11, 2023, through November 26, 2025, a total of 3786 patients with acute ischemic stroke underwent thrombectomy at the 14 participating stroke centers in Spain. Of these 3786 patients, 2776 (73%) fulfilled angiographic criteria, 440 (12%) were randomized, and 433 (11%) were included in the modified full analysis set. Seven patients in the thrombectomy plus intra-arterial alteplase group were excluded from the modified full analysis because the study treatment was not initiated (Figure 1).

Of the 433 patients in the modified full analysis set population, 214 were randomly assigned to undergo thrombectomy plus intra-arterial alteplase and 219 were randomly assigned to undergo thrombectomy alone. The median age of the 433 patients was 76 years (IQR, 75-78 years), 221 patients (51%) were women, and 35 patients (8%) were from 19 different countries outside Spain. The median age in the thrombectomy plus intra-arterial alteplase group was 2 years higher than in the thrombectomy alone group.

Other baseline characteristics were similar between treatment groups. The study population resembled other urban stroke populations in Europe (**Table 1** and eTable 4 in Supplement 4). There were missing patient data for some of the key variables (eTable 5 in Supplement 4). An overview of the major protocol deviations appears in eTable 6 in Supplement 4. The enrollment rates by center and overall appear in eTable 7 and eFigure 1, respectively, in Supplement 4. The median NIHSS score was 15 (IQR, 15-20) and the median ASPECTS was 10 (IQR, 8-10). Intravenous thrombolysis was administered before thrombectomy to 274 patients (63%), including intravenous alteplase to 192 patients and intravenous tenecteplase to 82 patients.

At randomization, the expanded TICI score was 2b50 in 13 patients (3%), 2b67 in 85 patients (20%), 2c in 86 patients (20%), and 3 in 249 patients (58%). The median time from stroke onset to randomization was 275 minutes (IQR, 189-575 minutes), the median time from stroke onset to the initiation of the study treatment was 280 minutes (IQR, 200-582 minutes), and the median duration of the thrombectomy procedure was 32 minutes (IQR, 23-46 minutes). There were no significant between-group differences in these measures or in the incidence of procedure-related complications after randomization (eTable 8 in Supplement 4).

Primary and Secondary Outcomes

The results for the primary outcome appear in **Figure 2** and **Table 2**. At 90 days, 57.5% of patients (123/214) in the thrombectomy plus intra-arterial alteplase group had an mRS score of 0 or 1 (excellent outcome) compared with 42.5% of patients (93/219) in the thrombectomy alone group (adjusted risk difference, 15.0% [95% CI, 5.7%-24.3%]; $P = .002$). The results of the prespecified and post hoc subgroup analyses of excellent functional outcome (mRS score of 0 or 1) at 90 days appear in eFigure 2 in Supplement 4. At 90 days, data on mRS score were missing for 1 patient (0.2%). This patient was known to be alive within the prespecified assessment window and was assigned an mRS score of 4 according to the prespecified hierarchical imputation strategy.

The results were unchanged in a post hoc sensitivity analysis using multiple imputation (risk difference, 14.9% [95% CI, 5.6%-24.3%]; $P = .002$, consistent with the primary analysis). In prespecified subgroup analyses, the risk difference in favor of thrombectomy plus intra-arterial alteplase was directionally consistent across all subgroups, and there were no significant treatment assignment × baseline characteristic (clinical or procedural) interactions.

For the secondary outcomes, residual hypoperfusion on follow-up perfusion imaging was observed in 55 of 192 patients (28.6%) in the thrombectomy plus intra-arterial alteplase group compared with 96 of 190 patients (50.5%) in the thrombectomy alone group (adjusted risk difference, −22.0% [95% CI, −31.5% to −12.4%]; $P < .001$). Vessel reocclusion was identified in 5 patients in the thrombectomy plus intra-arterial alteplase group compared with 2 patients in the thrombectomy alone group (eTable 8 in Supplement 4).

In a post hoc sensitivity analysis adjusting for time from randomization to CT perfusion acquisition, the treatment effect remained unchanged (adjusted risk difference, −21.8% [95% CI, −31.4% to −12.3%]; $P < .001$). Time from randomization to imaging was not independently associated with residual hypoperfusion. In a model including a treatment

Table 1. Baseline Patient Characteristics

	Thrombectomy plus intra-arterial alteplase (n = 214)[a]	Thrombectomy alone (n = 219)[a]
Demographics		
Age, median (IQR), y	77 (67-83)	75 (66-83)
Sex		
Male	100 (46.7)	112 (51.1)
Female	114 (53.2)	107 (48.9)
Medical history		
Hypertension	151 (70.6)	131 (59.8)
Diabetes	46 (21.4)	53 (24.2)
Atrial fibrillation	47 (22.0)	46 (21.0)
Prior ischemic stroke or transient ischemic attack	19 (8.8)	21 (9.6)
Prestroke modified Rankin Scale score		
0	173 (80.8)	175 (79.9)
1	41 (19.2)	44 (20.1)
Cause of stroke[b]		
Large artery atherosclerosis	13 (6.1)	13 (5.9)
Cardioembolic	106 (49.5)	106 (48.4)
Other reason	47 (22.0)	37 (16.9)
Unknown reason	48 (22.4)	63 (28.8)
NIHSS score at hospital admission, median (IQR)[c]	15 (10-20)	15 (11-15)
Received intravenous thrombolysis treatment before randomization	136 (63.5)	138 (63.0)
Laboratory and radiological findings		
Glucose level, median (IQR), mg/dL	120 (106-148)	123 (104-146)
Exanded TICI scores at randomization[d]		
2b50 (50%-66% reperfusion)	3 (1.4)	10 (4.6)
2b67 (67%-89% reperfusion)	54 (25.2)	31 (14.2)
2c (90%-99% reperfusion)	40 (18.7)	46 (21.0)
3 (100% reperfusion)	117 (54.7)	132 (60.3)
ASPECTS, median (IQR)[e]	9 (8-10)	10 (9-10)
Event timing		
Time from the last known well, median (IQR), min		
To randomization	266 (189-570)	281 (187-572)
To start of study treatment, min (n = 213)	280 (200-582)	
Time from femoral puncture to randomization, median (IQR), min	31 (24-46)	34 (23-46)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT (computed tomography) Score; NIHSS, National Institutes of Health Stroke Scale; TICI, Treatment in Cerebral Ischemia.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Classified according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.

[c] Scores range from 0 to 42; higher scores indicate more severe neurological deficits.

[d] Core laboratory assessment score.

[e] Imaging measure of the extent of ischemic stroke. Scores range from 0 to 10; higher scores indicate a smaller infarct core. The values were calculated at the central core laboratory.

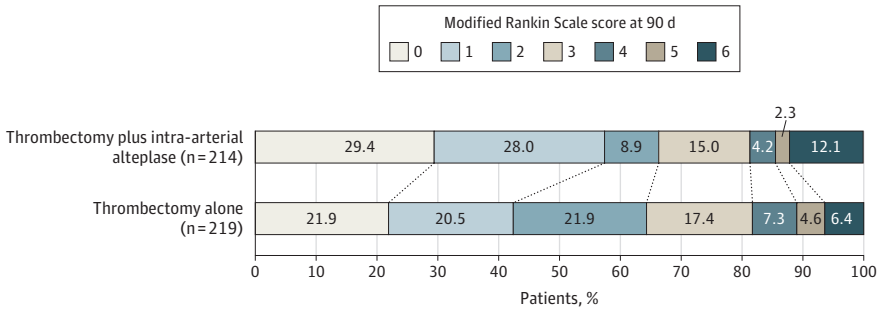
assignment × time to imaging interaction term, no significant interaction was observed, suggesting that the treatment effect did not vary according to imaging timing.

The volume of hypoperfusion and the infarct expansion ratio did not differ significantly between the thrombectomy plus intra-arterial alteplase group and the thrombectomy alone group (Table 2). The results were consistent in the sensitivity analyses (eTable 3 in Supplement 4).

In the prespecified secondary ordinal (shift) analysis of mRS scores at 90 days, the proportional odds assumption was violated, indicating nonuniform effects across mRS thresholds; accordingly, the common odds ratio is not interpretable as constant. The prespecified stratified van Elteren test showed no significant between-group difference.

In the prespecified modified full analysis set, in which patients who died before 90 days were assigned a Barthel Index score of 0, there was no significant between-group difference at 90 days (Table 2). Thrombectomy plus intra-arterial alteplase was associated with significantly higher EQ-5D-5L scores at 90 days (Table 2).

Figure 2. Component Bar Graph Depicting the Distribution of Modified Rankin Scale Scores at Day 90 in the Full Analysis Set



Patients were evaluated by central assessors. The scores range from 0 to 6 (0 indicates no symptoms; 1, no clinically significant disability; 2, slight disability [able to handle own affairs without assistance but unable to carry out all previous activities]; 3, moderate disability [require some help but able to walk unassisted]; 4, moderately severe disability [unable to attend body needs and unable to walk]; 5, severe disability [require constant nursing care and attention]; and 6, death). The scores of 5 and 6 were combined for the analysis. Treatment with intra-arterial alteplase was associated with a favorable outcome (a score of 0 or 1 on the modified Rankin Scale) at 90 days (adjusted risk difference, 15.0% [95% CI, 5.7%-24.3%]; *P* = .002). The between-group difference in the overall distribution of scores was not statistically significant.

Table 2. Primary and Secondary Outcomes

	Thrombectomy plus intra-arterial alteplase (n = 214)	Thrombectomy alone (n = 219)	Adjusted risk difference, % (95% CI)	*P* value[a]
Primary outcome				
Modified Rankin Scale score of 0 to 1 at 90 d, No. (%)	123 (57.5)	93 (42.5)	15.0 (5.7 to 24.3)	.002
Secondary outcomes				
Hypoperfusion at 36 h, No. (%)[b,c]	55 (28.6)	96 (50.5)	−22.0 (−31.5 to −12.4)	<.001
Volume of hypoperfusion at 36 h, adjusted mean (95% CI), mL[c]	5.0 (3.7 to 6.6)	6.1 (4.5 to 8.2)	0.82 (0.55 to 1.23)[d]	.34[e]
Infarct expansion ratio, adjusted mean (95% CI)[c,f]	56.6 (42.9 to 74.6)	65.4 (49.6 to 86.2)	0.87 (0.59 to 1.28)[c]	.47
Barthel Index 95 to 100 at 90 d, No. (%)[g]	136 (63.6)	128 (58.4)	5.1 (−4.1 to 14.3)	.28
Self-reported EQ-5D-5L score at 90 d, median (Q1:Q3) [IQR][h]	0.9 (0.7:1.0) [0.3]	0.8 (0.7:1.0) [0.3]	0.07 (0.01 to 0.12)[i]	.02
Modified Rankin Scale score at 90 d[j]				.08[k]

Abbreviation: EQ-5D-5L, EuroQol 5-Dimension 5-Level.

[a] From binomial regression model unless otherwise specified.

[b] Delayed time greater than 3 seconds and comprising a minimum cluster size of 10 contiguous voxels.

[c] Analysis was based on available data only. Data were missing for 22 patients (10.3%) in the thrombectomy plus intra-arterial alteplase group and for 29 patients (13.2%) in the thrombectomy alone group.

[d] Data are expressed as ratio (%) of least-squares means (95% CI).

[e] From a γ regression model with a log link. A small constant (0.1) was added to accommodate observations with zero values.

[f] Refers to the ratio of final infarct volume to initial ischemic tissue volume.

[g] Scores range from 0 to 100 (higher scores indicate good performance on activities of daily living). A score between 95 and 100 indicates no disability that interferes with daily activities.

[h] Converts the 5-dimension health states into a single summary value. Scores range from −0.416 (health states worse than death) to 1.00 (full health); higher scores indicate better health-related quality of life.

[i] Adjusted median difference (95% CI).

[j] Assesses functional disability. Scores range from 0 (no symptoms) to 6 (death). The primary analysis was adjusted by previous use of alteplase as predefined.

[k] In the prespecified secondary ordinal (shift) analysis, the proportional odds assumption was violated (*P* = .003), indicating nonuniform effects across thresholds of the modified Rankin Scale; accordingly, the common odds ratio is not interpretable as constant. The prespecified stratified van Elteren test showed no significant between-group difference.

Safety Outcomes

Symptomatic intracranial hemorrhage occurred in 3 of 214 patients (1.4%) in the thrombectomy plus intra-arterial alteplase group compared with 1 of 219 patients (0.5%) in the thrombectomy alone group (adjusted odds ratio, 3.10 [95% CI, 0.32-30.0]; *P* = .33). Mortality at 90 days was 12.1% (26/214) in the thrombectomy plus intra-arterial alteplase group compared with 6.4% (14/219) in the thrombectomy alone group (adjusted risk difference, 5.9% [95% CI, 0.5%-11.3%], *P* = .03; **Table 3**). The results for procedure-related complications, deaths, and serious adverse events appear in eTable 8 through eTable 11 in Supplement 4.

Sensitivity Analyses

In a prespecified sensitivity analysis using alternative model specifications (including unadjusted models incorporating the treating center as a random effect), treatment with thrombectomy plus intra-arterial alteplase was associated with a favorable outcome compared with thrombectomy alone (eTable 12 in Supplement 4). The post hoc sensitivity analyses using a series of models considering baseline covariates that, by chance, might have some imbalance showed similar results and conclusions (eTable 13 in Supplement 4).

In a post hoc analysis, residual hypoperfusion was associated with a higher risk of an unfavorable functional outcome

Table 3. Severe Adverse Events

	Severe adverse events within 90 d, No. (%)	
	Thrombectomy plus intra-arterial alteplase (n = 214)	Thrombectomy alone (n = 219)
Primary safety outcomes		
Death at 90 d	26 (12.1)	14 (6.4)
Symptomatic intracranial hemorrhage at 36 h	3 (1.4)	1 (0.5)
Additional safety outcomes		
Any serious adverse events at 90 d	61 (28.5)	55 (25.1)
Parenchymal hematoma at 36 h		
Type I[a]	13 (6.1)	9 (4.1)
Type II[b]	4 (1.9)	4 (1.8)
Subarachnoid hemorrhage at 36 h	13 (6.1)	13 (5.9)
Hemorrhagic infarction at 36 h		
Type I[c]	7 (3.3)	9 (4.1)
Type II[d]	15 (7.0)	9 (4.1)
Any asymptomatic intracranial hemorrhage at 36 h	52 (24.3)	44 (20.1)

[a] Blood clots not exceeding 30% of the infarcted area with some mild space-occupying effects.

[b] Dense blood clots exceeding 30% of the infarct volume with significant space-occupying effects.

[c] Small petechiae along the margins of the infarct.

[d] More confluent petechiae within the infarcted area without space-occupying effects.

(mRS scores of 2 to 6) than no hypoperfusion (adjusted risk difference, 11.0% [95% CI, 1.0% to 21.0%]). In a post hoc analysis of patients who had an expanded TICI score of 3 (as assessed by the central core laboratory), residual hypoperfusion was observed in 28 of 192 patients (14.6%) in the thrombectomy plus intra-arterial alteplase group compared with 49 of 190 patients (25.8%) in the thrombectomy alone group (adjusted risk difference, −11.3% [95% CI, −19.3% to −3.3%]; P = .006). Sensitivity analyses using multiple imputation yielded similar results for the 3 neuroimaging outcomes (eTable 3 in Supplement 4).

Discussion

In this multicenter randomized trial, adjunctive intra-arterial alteplase administered to patients with acute ischemic stroke immediately after successful thrombectomy for anterior circulation large vessel occlusion was associated with a higher likelihood of excellent functional recovery at 90 days than thrombectomy alone. The absolute difference of 15.0% (corresponding to a number needed to treat of 7) was consistent across prespecified subgroups of patients defined by demographic, clinical, and procedural characteristics, supporting the robustness of the primary finding. These findings are consistent with the results from the CHOICE[6] and PEARL[8] randomized clinical trials, which evaluated intra-arterial alteplase after successful thrombectomy.

Secondary imaging outcomes showed that patients treated with thrombectomy plus intra-arterial alteplase had lower rates of residual hypoperfusion on CT perfusion imaging than those who received thrombectomy alone, although hypoperfusion volumes were not smaller. In post hoc analyses, residual hypoperfusion was associated with a higher risk of an unfavorable functional outcome at 90 days. In post hoc analyses, patients with complete angiographic recanalization (expanded TICI score of 3) had significantly higher rates of residual hypoperfusion on CT perfusion imaging with thrombectomy alone than with thrombectomy plus intra-arterial alteplase.

These findings suggest that achieving complete tissue-level reperfusion beyond angiographic recanalization of the target vessel may be relevant to clinical outcomes in patients treated with adjunctive thrombolytic therapy. The lack of a significant between-group difference in hypoperfusion volume suggests that a subset of patients may be resistant to adjunctive thrombolytic therapy. Whether alternative dosing strategies or patient-selection approaches could influence this response requires further study.

No significant between-group difference was observed in the ordinal shift analysis of mRS scores at 90 days, a finding that was not consistent with the primary outcome. Because all patients had successful recanalization before randomization, both groups were likely predisposed to a favorable recovery. In this context, thrombectomy plus intra-arterial alteplase may primarily enhance microvascular perfusion, yielding modest gains concentrated in the mRS score range of 0 to 1 rather than broader shifts across the scale. Notably, distinctions between adjacent categories, especially an mRS score of 1 vs 2, remain clinically important because patients with an mRS score of 0 or 1 have the ability to return to full-time work, school, and leisure activities.[15]

The effect on the Barthel Index at 90 days did not reach statistical significance, whereas thrombectomy plus intra-arterial alteplase was associated with significantly higher EQ-5D-5L scores. Findings from the secondary functional and patient-reported outcome measures were concordant with this overall pattern, although these findings were exploratory and should be interpreted cautiously.

Infarct expansion did not differ consistently between groups. The apparent dissociation between improved perfusion on imaging and the absence of measurable differences in infarct growth may reflect the limited sensitivity of noncontrast CT for detecting subtle or spatially heterogeneous changes in tissue injury. Future studies evaluating adjunctive therapies after thrombectomy may benefit from incorporating more

sensitive imaging biomarkers to better characterize treatment effects at the tissue level.

In the current trial, symptomatic intracranial hemorrhage was rare. Although the estimated risk was numerically higher in the thrombectomy plus intra-arterial alteplase group than in the thrombectomy alone group, no statistically significant between-group differences were observed. All-cause mortality at 90 days was low overall; however, mortality was significantly higher in the thrombectomy plus intra-arterial alteplase group. Importantly, the causes of death were heterogeneous and did not indicate an excess of events typically attributable to thrombolytic therapy. Only 1 death was adjudicated as related to the study medication, and the majority of deaths occurred beyond the first week after treatment, reducing the likelihood of a direct causal relationship with early procedural or pharmacological complications.

These findings should be interpreted in the context of the broader evidence base. A recent systematic review and meta-analysis[16] of 6 randomized clinical trials including 1971 patients who underwent thrombectomy with or without adjunctive intra-arterial thrombolysis demonstrated no difference in 90-day mortality (18.3% vs 18.3%, respectively; risk ratio, 1.00 [95% CI, 0.83-1.21]; $P = .99$, $I^2 = 0\%$), and no significant increase in symptomatic intracranial hemorrhage (5.06% vs 4.48%; risk ratio, 1.14 [95% CI, 0.76-1.70]; $P = .53$). These pooled results provide reassuring evidence regarding the safety profile of intra-arterial thrombolysis and suggest that the mortality imbalance observed in the current trial may reflect random variation rather than a treatment-related effect.

Taken together, the available data support a cautious and measured interpretation of the safety outcomes in the current trial. Clarifying the potential influence of adjunctive intra-arterial alteplase on mortality will require additional evidence, including the results of ongoing trials and pooled individual-level patient analyses. Furthermore, future studies should examine whether racial and ethnic differences, which are currently underrepresented in the available data, modify complication rates or treatment effects because these factors may have important implications for generalizability and equity in stroke care.

The strengths of this trial include its randomized, multicenter design, centralized blinded assessment of outcomes, and the use of a standardized protocol for administration of intra-arterial alteplase. The inclusion of a substantial proportion of patients with complete angiographic reperfusion (expanded TICI score of 3), along with patients who had received prior intravenous thrombolysis, and a balanced representation of males and females, enhances the relevance of the findings to contemporary endovascular practice. Although adjunctive thrombolysis has been proposed primarily for patients with angiographically evident distal emboli or impaired distal perfusion,[17] the treatment effect was not attenuated among patients with complete angiographic reperfusion.

Microvascular hypoperfusion was observed in approximately one-quarter of patients with cerebral angiograms classified as not having any identifiable proximal arterial abnormality that could account for the hypoperfusion, suggesting a microvascular contribution. These observations are consistent with the mechanistic hypothesis underlying the current trial and underscore the limitations of conventional angiography in assessing tissue-level reperfusion. The benefit of intra-arterial alteplase was preserved among patients who had received prior intravenous thrombolysis, suggesting complementary effects without increased hemorrhagic risk and no evidence of heterogeneity for the treatment effect by sex.

Adjunctive intra-arterial alteplase administration after successful thrombectomy was associated with a higher rate of excellent functional outcome and patient-reported health-related quality of life at 90 days, and fewer residual perfusion abnormalities on CT perfusion imaging without an increase in symptomatic intracranial hemorrhage and with consistent absolute treatment differences across prespecified subgroups. Mortality was higher in the thrombectomy plus intra-arterial alteplase group and this result warrants further investigation. However, in the context of randomized evidence, including recent meta-analytic data, no significant increase in mortality has been observed with intra-arterial thrombolysis.

These findings suggest that pharmacological strategies targeting tissue-level reperfusion may be associated with incremental benefit, including in patients with complete angiographic normalization, and support further study to refine patient selection and optimize treatment strategies.

Limitations

Several limitations warrant consideration. First, the open-label design introduces the potential for bias, although the functional outcomes were centrally assessed by investigators who were unaware of treatment assignment. Placebo administration was not feasible because, at the time of trial initiation, the manufacturer of alteplase prioritized active-drug production in response to a continent-wide shortage of thrombolytic agents. Second, the use of noncontrast CT limits the sensitivity for accurate volumetric measurements and detection of subtle infarct progression.

Third, the incomplete documentation of screening exclusions may have introduced selection bias and may limit the generalizability of the findings. Although the trial was conducted within a single national health system with relatively uniform standards of care, which may limit generalizability to other settings, the inclusion of patients from 19 countries in addition to Spain may provide some support for the broader applicability of the findings. Caution is warranted when extrapolating these findings to more diverse populations. Fourth, residual baseline imbalances could have influenced outcomes; however, post hoc adjustments did not materially alter the results.

Conclusions

Among patients with acute ischemic stroke and successful thrombectomy, adjunctive intra-arterial alteplase increased

theproportion achieving excellent functional outcome at 90 days without a significant increase in symptomatic intracranial hemorrhage. Higher mortality in the thrombectomy plus intra-arterial alteplase group warrants further study.

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