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Effect of Direct Transportation to Thrombectomy-Capable Center vs Local Stroke Center on Neurological Outcomes in Patients With Suspected Large-Vessel Occlusion Stroke in Nonurban Areas
The RACECAT Randomized Clinical Trial

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IMPORTANCE In nonurban areas with limited access to thrombectomy-capable centers, optimal prehospital transport strategies in patients with suspected large-vessel occlusion stroke are unknown.

OBJECTIVE To determine whether, in nonurban areas, direct transport to a thrombectomy-capable center is beneficial compared with transport to the closest local stroke center.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, population-based, cluster-randomized trial including 1401 patients with suspected acute large-vessel occlusion stroke attended by emergency medical services in areas where the closest local stroke center was not capable of performing thrombectomy in Catalonia, Spain, between March 2017 and June 2020. The date of final follow-up was September 2020.

INTERVENTIONS Transportation to a thrombectomy-capable center (n = 688) or the closest local stroke center (n = 713).

MAIN OUTCOMES AND MEASURES The primary outcome was disability at 90 days based on the modified Rankin Scale (mRS; scores range from 0 [no symptoms] to 6 [death]) in the target population of patients with ischemic stroke. There were 11 secondary outcomes, including rate of intravenous tissue plasminogen activator administration and thrombectomy in the target population and 90-day mortality in the safety population of all randomized patients.

RESULTS Enrollment was halted for futility following a second interim analysis. The 1401 enrolled patients were included in the safety analysis, of whom 1369 (98%) consented to participate and were included in the as-randomized analysis (56% men; median age, 75 [IQR, 65-83] years; median National Institutes of Health Stroke Scale score, 17 [IQR, 11-21]); 949 (69%) comprised the target ischemic stroke population included in the primary analysis. For the primary outcome in the target population, median mRS score was 3 (IQR, 2-5) vs 3 (IQR, 2-5) (adjusted common odds ratio [OR], 1.03; 95% CI, 0.82-1.29). Of 11 reported secondary outcomes, 8 showed no significant difference. Compared with patients first transported to local stroke centers, patients directly transported to thrombectomy-capable centers had significantly lower odds of receiving intravenous tissue plasminogen activator (in the target population, 229/482 [47.5%] vs 282/467 [60.4%]; OR, 0.59; 95% CI, 0.45-0.76) and significantly higher odds of receiving thrombectomy (in the target population, 235/482 [48.8%] vs 184/467 [39.4%]; OR, 1.46; 95% CI, 1.13-1.89). Mortality at 90 days in the safety population was not significantly different between groups (188/688 [27.3%] vs 194/713 [27.2%]; adjusted hazard ratio, 0.97; 95% CI, 0.79-1.18).

CONCLUSIONS AND RELEVANCE In nonurban areas in Catalonia, Spain, there was no significant difference in 90-day neurological outcomes between transportation to a local stroke center vs a thrombectomy-capable referral center in patients with suspected large-vessel occlusion stroke. These findings require replication in other settings.

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Prehospital transport for patients with suspected acute stroke have traditionally consisted of dispatch to the closest hospital. In patients with acute stroke due to large -vessel occlusion (LVO), thrombectomy is associated with a higher rate of favorable outcome than intravenous thrombolysis alone,[1-5] and its benefit is strongly time dependent.[6]

Nonrandomized studies suggest that patients treated with thrombectomy who are initially brought to thrombectomy-capable centers have better outcomes compared with those who are secondarily transferred from local stroke centers.[7,8] In some regions, these findings led to a redesign of prehospital stroke systems of care whereby it is recommended that patients with suspected LVO who are within a 30- to 60-minute transportation time to a thrombectomy-capable referral center bypass the closest local stroke center to avoid time delays associated with interhospital transfers.[9-11]

This approach may have theoretical disadvantages: intravenous thrombolysis may be delayed or denied because of longer transport times, and unnecessary transport of patients without an LVO ischemic stroke to thrombectomy-capable centers could lead to inadequate resource utilization, overcapacity issues, increased costs, and patient inconvenience.

For on-scene identification of patients with an LVO ischemic stroke by prehospital emergency medical services (EMS) clinicians, several prehospital scales have been developed that have different degrees of accuracy.[12] The Rapid Arterial Occlusion Evaluation (RACE) Scale (with scores ranging from 0 [no findings] to 9 [severe neurological impairment]; see eFigure 1 in Supplement 1) has undergone extensive validation showing a high discrimination capacity to identify patients with LVO.[12-14]

The RACECAT (Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory) trial aimed to evaluate whether patients in nonurban areas of Catalonia with a suspected severe acute stroke had better outcomes if they were directly transported to a thrombectomy-capable center, bypassing the closest local stroke center.

Key Points

Question In patients experiencing suspected large-vessel occlusion stroke in a nonurban area, is there a difference in neurological outcomes between those who are transported to the closest local stroke center vs directly to a thrombectomy-capable referral center?

Findings In this randomized clinical trial that included 1401 patients with suspected large-vessel occlusion stroke in nonurban Catalonia, Spain, transportation to a thrombectomy-capable referral center vs a local stroke center resulted in an odds ratio of 1.03 for reduced disability at 90 days, as measured by the modified Rankin Scale. This was not statistically significant.

Meaning In nonurban areas in Catalonia, Spain, where the closest hospital was not capable of performing thrombectomy, there was no significant difference in 90-day neurological outcomes between patients transported to a local stroke center first vs directly to a thrombectomy-capable referral center in patients with suspected large-vessel occlusion acute ischemic stroke; these findings require replication in other settings.

Methods

Study Design

RACECAT[15] was a spatial-temporal cluster-randomized trial, with blinded end-point assessment, embedded within a mandatory registry of patients with stroke[16] (eFigure 2 in Supplement 1). Across the subset of patients triaged in nonurban areas, 2 EMS routing strategies were compared according to a preestablished concealed temporal sequence:

- Strategy 1: transport to the closest local stroke center with no thrombectomy capabilities. For patients with confirmed/suspected LVO, after initial evaluation in local stroke centers, subsequent transfer to a thrombectomy-capable center was organized. Time to admission to a thrombectomy-capable center was determined by the sum of the time periods from onset to first hospital arrival; door-in, door-out; and interhospital transfer.
- Strategy 2: direct transport to a thrombectomy-capable center. Time to admission was determined by transport time to the allocated thrombectomy-capable center.

The study protocol was approved by a central ethics committee and by the research board at each participating center. All patients or surrogates provided deferred written informed consent. The trial protocol and statistical analysis plan are available in Supplement 2 and Supplement 3, respectively.

Study Population

Patients were enrolled in the trial if they met the following inclusion criteria: (1) functionally independent, defined as a modified Rankin Scale (mRS) score between 0 and 2, as evaluated by EMS personnel in the field; (2) suspected acute stroke secondary to an LVO, defined as a RACE Scale score between 5 and 9; (3) evaluation by EMS personnel in a geographical areas where the primary referral center was a local stroke center without thrombectomy capabilities, covering a population of 3.85 million; and (4) estimated arrival at a thrombectomy-capable center less than 7 hours after symptom onset (for witnessed onset) or last time seen well. Patients were excluded if they had an unstable clinical status and/or coma requiring emergent life-support care (eTable 1 in Supplement 1). Transport time to a thrombectomy-capable center ranged from 20 to 180 minutes.

All patients enrolled in the trial were included in the safety analysis. Only patients who gave deferred informed consent were considered for the as-randomized population analysis for the outcomes concerning this population. The target population, in which the primary hypothesis was tested, included patients with confirmed discharge diagnosis of ischemic stroke or transient ischemic attack/averted stroke (for cases in which symptoms resolved after randomization spontaneously or after reperfusion treatment,

respectively). The rationale for choosing this population was that the intervention of the trial was specifically suited to reduce treatment delays in patients who are evaluated for thrombectomy.[17]

This trial was performed in Catalonia, with participation of EMS and all stroke centers involved in acute stroke care, which included 6 thrombectomy-capable centers and 22 local stroke centers (including 8 primary stroke centers and 14 telestroke centers), from March 2017 to June 2020 (eFigure 3 in Supplement 1). Telestroke centers are capable of initiating intravenous thrombolysis after consultation with a certified stroke neurologist through telemedicine. Primary stroke centers have an on-site neurologist and can admit patients into a stroke unit. During the last months of the study, 3 primary stroke centers started performing thrombectomy during working shifts. For the purpose of the trial, during working hours when thrombectomy was available in these centers, patients located in their primary catchment area were not included, and these centers operated as thrombectomy-capable centers for the nearby geographical area covered by other local stroke centers. During nonworking hours, when thrombectomy was not available at these centers, these centers operated as local stroke centers, and the entire population located in their catchment area was considered for inclusion. Only 8 patients included in the trial received thrombectomy at these centers, representing less than 2% of patients treated with thrombectomy (eFigure 4 in Supplement 1).

Prenotification criteria for the EMS coordination center were established to provide high sensitivity in identifying trial candidates: RACE Scale score greater than 3 and time from symptom onset to EMS evaluation of less than 8 hours. If these conditions were met, EMS personnel contacted a consulting stroke neurologist via telephone call. If the stroke neurologist confirmed all eligibility criteria, the patient was enrolled in the trial (eFigure 5 in Supplement 1). Air travel via helicopter was used for interhospital transfers rarely in patients located in remote areas when conditions permitted.

Randomization

A cluster design was chosen to facilitate the logistics of patient inclusion, to avoid possible delays in care caused by individual randomization, and to obtain informed consent. Transport allocation to each of the 2 intervention groups was adjudicated in a 1:1 ratio according to a temporal cluster design: a predefined randomized calendar of 12-hour time slots was previously established, stratified by territory (metropolitan vs provincial area) and day of the week (weekday vs weekend). Assignment to 1 of the 2 possible transport options was performed in real time by a smartphone-based system, linked to the preestablished randomized schedule, which was otherwise unknown to all investigators and professionals involved in the care of participants. Immediately after allocation, the stroke neurologist alerted the allocated destination to the upcoming arrival of the patient.

An inadvertent mismatch between randomization list and allocation occurred for the initial 350 patients. The company that parameterized the allocation sequence did not include the provided randomization code in the algorithm. Patients were allocated in an alternating sequence within each block that allocated the routing group for each new patient, instead of following the preplanned cluster groups. Despite the deviation between the randomization list and the allocation program, patients were allocated following a sequence that was de facto unpredictable for all investigators and EMS professionals. The mismatch was unnoticed by all investigators and only identified in an unplanned review of the randomization software due to a system software crash. The problem was resolved on identification and reported to the data safety and monitoring board, who determined that the trial was not substantively threatened (eAppendix 1 and eFigure 6 in Supplement 1).

Modification of Allocated Intervention

Modification of the initial transport allocation was allowed only when neurological deterioration or severe medical complications occurred during transport. In such a case, the patient was emergently transported to the closest stroke center. Deviations from initial destination due to other reasons were considered protocol deviations (**Figure 1**; eTable 2 in Supplement 1).

Concomitant Care and Interventions Prohibited During the Trial

Other than the initial decision about the first transport option, patients received standard clinical care and endovascular treatment was indicated according to institutional protocols, agreeing with European Stroke Organisation guidelines.

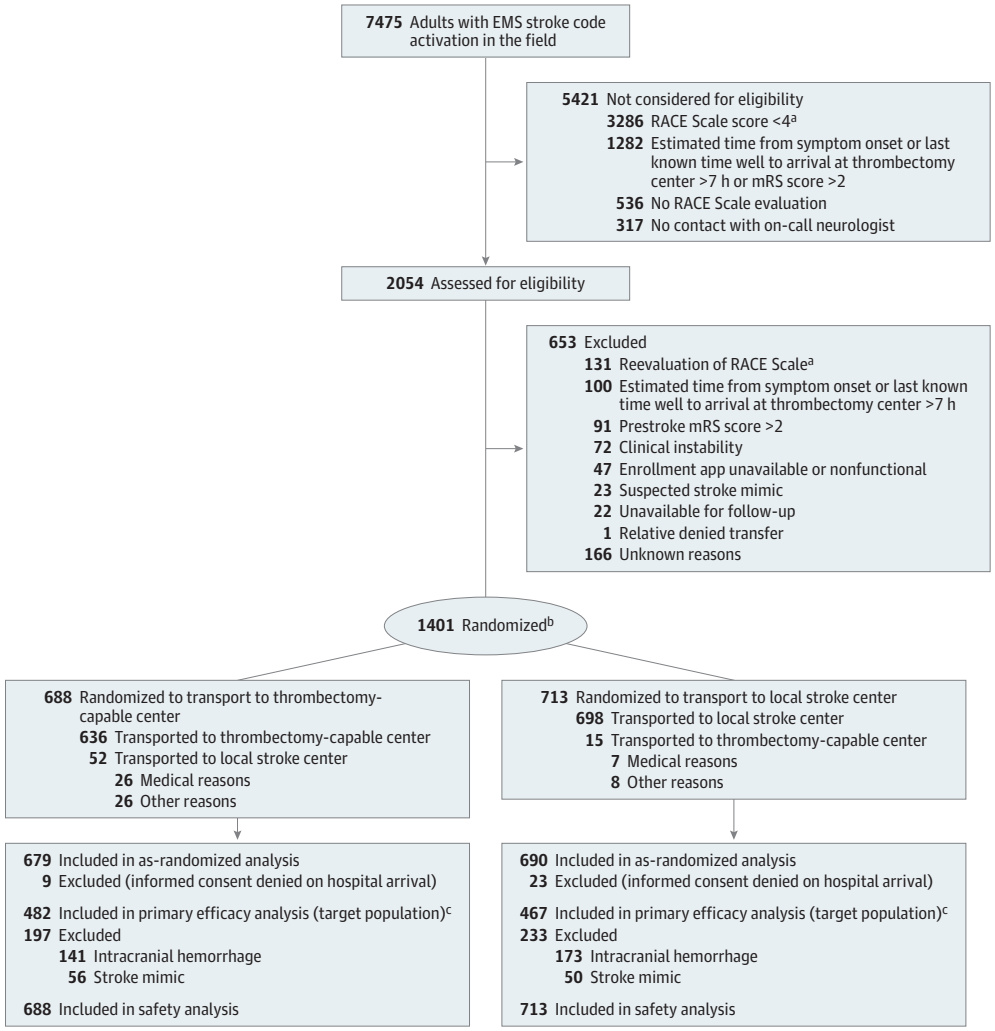
In local stroke centers, all patients were evaluated by an on-site neurologist or through telemedicine consultation, according to the type of stroke center. Patients with a confirmed LVO on vascular imaging or, if imaging was not available, with a clinical suspicion of LVO (National Institutes of Health Stroke Scale [NIHSS] score ≥6) were considered for thrombectomy and transferred to the thrombectomy-capable referral center.

Outcomes

The primary outcome was disability at 90 days, as assessed by the mRS, with scores ranging from 0 (no symptoms) to 6 (death), at the individual participant level in the target population. The primary outcome of the trial was centrally evaluated through a structured telephone-based interview[17] by certified assessors (n = 2) blinded to group assignment.

Secondary outcomes included (1) disability at 90 days in the as-randomized population; (2) disability at 90 days in patients with intracranial hemorrhage; (3) disability at 90 days in the following subgroups: age, sex, tissue plasminogen activator (tPA) eligibility (within 4 hours after onset, when attended by EMS, and no anticoagulation therapy), baseline mRS score (confirmed at the hospital) and RACE Scale score; (4) rates of intravenous tPA among the target population; (5) rates of thrombectomy among the target population; (6) times from stroke onset to intravenous tPA administration among the target population; (7) times from stroke onset to thrombectomy initiation among the target population;

Figure 1. Participant Flow Through the RACECAT Trial



EMS indicates emergency medical services; mRS, modified Rankin Scale.

[a] The Rapid Arterial Occlusion Evaluation (RACE) Scale ranges from 0 to 9 (lower to higher stroke severity, respectively; see eFigure 1 in Supplement 1). A score greater than 4 was the cut point to identify patients with a large-vessel occlusion. EMS personnel contacted a neurologist if the RACE Scale score was greater than 3 to provide high sensitivity in identifying trial candidates, although a score greater than 4 was considered the inclusion criterion.

[b] Randomization into 1 of the 2 intervention groups was carried out in real time by a smartphone-based app in a 1:1 ratio according to a temporal cluster design. Written informed consent was obtained after patients arrived at the hospital.

[c] The target population, in which the primary hypothesis was tested, included patients with confirmed diagnosis at discharge of ischemic stroke or transient ischemic attack/averted stroke.

(8) rate of dramatic early favorable response at 24 hours (defined as an NIHSS score ≤2 or ≥8-point improvement from baseline in the NIHSS score) among the target population; (9) rate of dramatic early favorable response at 24 hours among patients with intracranial hemorrhage (not reported herein); (10) inflection point with respect to time from stroke onset to EMS attendance (not reported herein) and estimated transport time to thrombectomy-capable referral center beyond which the transport destination confers differences on neurological outcomes; and (11) difference in mean cost of care at 90 days in all patients (not reported herein). Prespecified safety outcomes included (1) mortality at 90 days in the as-randomized population; (2) mortality at 90 days in the subgroup of patients with intracranial hemorrhage; (3) rate of clinical deterioration requiring intubation during initial transport; (4) clinical worsening at 24 hours after stroke onset (defined as a worsening of ≥4 points in the NIHSS score compared with baseline) in the as-randomized population.

Safety analyses were evaluated by the data safety and monitoring board after inclusion of the first 100 patients and thereafter every additional 300 patients.

Transport group allocation could not be blinded, and investigators, who were not blinded to the assigned group, registered secondary outcomes (risk of evaluation bias).

Time Metrics

Observed workflow times were recorded. To calculate travel distances and compute estimated time intervals after treatment

allocation, a mapping application was developed using the Google Maps Distance Matrix Application Programming Interface traffic model parameter. For each patient, stroke onset location, closest local stroke center, and thrombectomy-capable referral center geographic coordinates were linked to the application. Computed times were estimated according to historical conditions and traffic information at the time that patients were evaluated.

Sample Size Calculation

Because patients with ischemic stroke constitute the target population, sample size calculation was based on the enrichment studies paradigm. As the expected ischemic stroke and nonischemic stroke ratio was 3:1, the recruited sample was increased accordingly. The hypothesis of the study was that direct transport to a thrombectomy-capable center would lead to an estimated difference in the rate of good functional outcome of 6% or more, corresponding to an odds ratio (OR) of 1.35 for improvement. This estimation was based on previous reports that demonstrated that bypassing local stroke centers would increase the rate of thrombectomy by 15% to 20%,[18] thus increasing the odds of good functional outcome. A triangular test with 2 interim looks (40%/70% of sample recruitment) plus 1 final analysis was specified with values of a = 1.7048 and v1 = 42.2291. Total sample size, including patients with nonischemic stroke who would not be included in the final efficacy analysis, was estimated to be 1754 (eFigure 7 in Supplement 1).

Statistical Analysis

In the primary analyses, patients were analyzed according to their randomization group. Missing data on the primary outcome (mRS score at 90 days) were handled with the use of the last-observation-carried-forward approach for patients known to be alive at 90 days, and the worst outcome (mRS score of 6) was assigned for patients in whom vital status was unknown.

The primary outcome was tested using cumulative ordinal logistic regression to estimate the common OR and 95% CIs of the shift analysis on the mRS[19] at 90 days (with scores of 5 [severe disability] and 6 [death] collapsed into a single group[20]) in the target population (final diagnosis of ischemic stroke or transient ischemic attack/averted stroke), with a 2-sided $P < .05$ considered statistically significant. For the primary analysis and all other outcome analyses that evaluated the shift analysis on the mRS score, regression models that are unadjusted and adjusted by stratifying factors (time slot, territory, and day of week), RACE Scale score, and age are reported. The proportional odds assumption on the primary outcome analysis was tested using a Brant test. The assumption of proportional odds was met, as no coefficient of the independent variables nor the omnibus achieved significance ($P > .05$ for all). As a post hoc analysis, the ordinal logistic regression model was replicated using a fully conditional specification multiple imputation method for missing mRS outcomes with 10 iterations and intervention group, age, sex, baseline mRS score, baseline NIHSS score, presence of LVO, thrombectomy, tPA administration, NIHSS score at 5 days, mRS score at 5 days, and time from onset to transport allocation as target variables for the imputation, as well as a mixed-effects model with clusters as a random effect to account for some of the potential biases introduced by small cluster sizes.

Prespecified secondary outcomes included a shift analysis on the mRS score at 90 days in the as-randomized population and in patients with intracranial hemorrhage and stroke mimic, which were tested as in the primary outcome. Among the target population, we estimated absolute differences and 95% CIs in the proportion of patients receiving intravenous tPA and thrombectomy. Median differences and 95% CIs, estimated using a bootstrapping method with 1000 samples, in time from symptom onset to tPA administration and thrombectomy initiation between intervention groups in the target population are reported. Prespecified subgroup analyses in the target population were performed to assess the potential effect modification of the association between direct transport to a thrombectomy-capable center and the primary outcome for age (<80 years vs ≥80 years), sex (male vs female), intravenous tPA treatment eligibility at randomization (estimated time to arrival at local stroke center <4 hours after stroke onset and no major contraindication to treatment), confirmed premorbid mRS score of 0 to 2 at hospital arrival, and initial RACE Scale score (5 to 7 vs 8 or 9). For each subgroup comparison, an interaction term between each specific subgroup and transport allocation adjusted by main effects, stratifying factors, age, and RACE Scale score was tested, and subgroup-specific associations and 95% CIs for the primary outcomes are reported. The consistency of the treatment effect according to estimated transport time to a thrombectomy-capable center was tested as a continuous variable with its interaction with transport allocation and adjusted by the same covariates as in subgroup analysis. As a post hoc analysis, the potential relationship between estimated transport time to a thrombectomy-capable center and clinical outcome was further analyzed selecting different time cut points derived from American Heart Association recommendations for prehospital routing in patients with suspected acute stroke.[10] Cut points selected were 30, 45, and 60 minutes; analyses were performed as in prespecified subgroup analyses.

Safety outcomes that evaluated mortality at 90 days in the safety population and in the subgroup of patients with intracranial hemorrhage were tested using a Cox proportional hazards models to estimate hazard ratios and 95% CIs. Proportional hazards assumption was supported by a nonsignificant relationship between scaled Schoenfeld residuals and time. Model estimates are reported unadjusted and adjusted for the same covariates as in the primary analysis. Absolute differences and 95% CIs in the rate of clinical deterioration during transport and clinical deterioration at 24 hours are reported.

For all outcomes, a 2-sided $P < .05$ was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All statistical analyses were performed using a standard software package (Stata version 12.0; StataCorp) and with R version 4.1 (R Foundation).

Table 1. Participant Characteristics and Workflow Measures[a]

Characteristics	Target population[b]		As-randomized population[c]	
	Thrombectomy-capable center (n = 482)	Local stroke center (n = 467)	Thrombectomy-capable center (n = 679)	Local stroke center (n = 690)
Age, median (IQR), y	77 (67-84)	76 (66-84)	76 (66-84)	74 (64-83)
Sex, No. (%)				
Female	219 (45.4)	209 (44.8)	293 (43.2)	308 (44.6)
Male	263 (54.6)	258 (55.2)	386 (56.8)	382 (55.4)
Travel time >60 min to a thrombectomy-capable center, No. (%)	270 (56.0)	254 (54.4)	376 (55.4)	378 (54.8)
Medical history, No. (%)				
Hypertension	352 (73.5)	331 (72.4)	478 (71.3)	476 (70.4)
Dyslipidemia	238 (49.7)	212 (46.4)	316 (47.2)	314 (46.4)
Diabetes	122 (25.5)	105 (23.0)	172 (25.7)	166 (24.6)
Atrial fibrillation	120 (25.1)	129 (28.2)	159 (23.7)	170 (25.1)
Prestroke anticoagulation treatment	90 (18.8)	82 (17.9)	121 (18.1)	118 (17.5)
Ischemic stroke or TIA	86 (18.0)	75 (16.4)	118 (17.6)	103 (15.2)
Coronary heart disease	83 (17.3)	65 (14.2)	100 (14.9)	81 (12.0)
Smoking	70 (14.6)	67 (14.7)	98 (14.6)	94 (13.9)
Peripheral vasculopathy	24 (5.0)	15 (3.3)	31 (4.6)	22 (3.3)
Prestroke modified Rankin Scale score 0-2, No. (%)[d]	435 (90.3)	426 (91.2)	618 (91.0)	636 (92.2)
RACE Scale[e]				
Median (IQR) score	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)
Score of 5-7, No. (%)	314 (65.3)	297 (63.6)	463 (68.3)	463 (67.1)
Score of 8-9, No. (%)	167 (34.7)	170 (36.4)	215 (31.7)	227 (32.9)
NIHSS score at hospital arrival, median (IQR)[f]	16 (9-20)	16 (11-21)	17.0 (11.0-21.0)	17.0 (11.0-21.0)
Blood pressure at first hospital arrival, median (IQR), mm Hg				
Systolic	151 (133-170)	150 (134-171)	153 (133-175)	153 (136-175)
Diastolic	82 (72-93)	82 (71-93)	83 (72-95)	84 (72-97)
Glucose level at hospital arrival, median (IQR), mg/dL	126 (108-156)	124 (108-152)	129 (109-162)	129 (109-160)
Wake-up stroke or unknown time since stroke onset, No. (%)	137 (28.6)	112 (24.5)	176 (26.3)	161 (23.8)
Clinical diagnosis on computed tomography at hospital arrival, No. (%)				
Ischemic stroke	470 (97.5)	450 (96.4)	470 (69.2)	450 (65.2)
TIA	12 (2.5)	17 (3.6)	12 (1.8)	17 (2.5)
Intracranial hemorrhage			141 (20.8)	173 (25.1)
Stroke mimic			56 (8.2)	50 (7.2)
Large-vessel occlusion detected at first hospital, No. (%)				
Yes	333 (69.1)	198 (43.4)		
No	138 (25.9)	62 (13.3)		
No determination	11 (2.3)	207 (44.3)		
Large-vessel occlusion detected at any hospital, No. (%)				
Yes	333 (69.1)	303 (64.9)		
No	137 (28.4)	116 (24.8)		
No determination	12 (2.5)	48 (10.3)		
Time from stroke onset to randomization, median (IQR), min	67 (44-164)	59 (40-111)	68 (45-148)	56 (42-126)
Time from randomization to first hospital arrival, median (IQR), min	61 (35-86)	21 (13-32)	59 (35-85)	22 (14-33)

(continued)

Table 1. Participant Characteristics and Workflow Measures[a] (continued)

Characteristics	Target population[b]		As-randomized population[c]	
	Thrombectomy-capable center (n = 482)	Local stroke center (n = 467)	Thrombectomy-capable center (n = 679)	Local stroke center (n = 690)
Time from stroke onset to first hospital arrival, median (IQR), min	142 (100-231)	88 (61-145)	140 (99-216)	91 (64-155)
Time from stroke onset to first hospital arrival <4 h, No. (%)	370 (76.8)	403 (86.3)	535 (78.8)	592 (85.8)
Transferred to thrombectomy-capable center, No. (%)		302 (64.6)		
Time from arrival to discharge at referral hospital (calculated in patients transferred), median (IQR), min		78 (63-97)		
Time from arrival at first hospital to intravenous alteplase administration, median (IQR), min	30 (22-40)	33 (25-48)		
Time from thrombectomy-capable center arrival to groin puncture, median (IQR), min	71 (49-97)	43 (32-59)		

Abbreviation: TIA, transient ischemic attack.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] Data on arterial occlusion and transport time to a thrombectomy-capable center were recorded only for patients with ischemic stroke, not for those with intracranial hemorrhage or stroke mimic. Thus, these data are not available for the as-randomized population.

[b] Patients with confirmed diagnosis of ischemic stroke or TIA/averted stroke.

[c] Patients with ischemic stroke, TIA/averted stroke, intracranial hemorrhage, and stroke mimic.

[d] The modified Rankin Scale assesses disability (with scores ranging from 0 [no symptoms] to 6 [death]) as described in eAppendix 2 in Supplement 1.

[e] The Rapid Arterial Occlusion Evaluation (RACE) Scale assesses stroke severity (with scores ranging from 0 [no findings] to 9 [severe neurological impairment]).

[f] The National Institutes of Health Stroke Scale (NIHSS) assesses stroke severity (with scores ranging from 0 [no symptoms] to 42 [severe symptoms]).

Results

The second interim analysis was performed as planned after 70% of patients (n = 1225) had completed 90 days of follow-up. The steering committee agreed with the data safety and monitoring board recommendation issued in June 2020 to stop recruitment because protocol-binding futility stopping boundaries were crossed (eFigure 7 in Supplement 1).

During the follow-up period and second interim analysis, inclusion of new patients continued, so that the final sample included a total of 1401 patients, who were evaluated for safety outcomes. After excluding 32 patients (2.28%) who denied informed consent, the as-randomized population was composed of 679 patients (49%) transported to thrombectomy-capable centers and 690 patients (51%) transported to local stroke centers. Major protocol deviations occurred in 92 patients (6.56%) (Figure 1; eTable 2 in Supplement 1). The mean number of patients per cluster was 1.2, making negligible the variance inflation effect (eFigure 5 in Supplement 1).

Baseline Characteristics

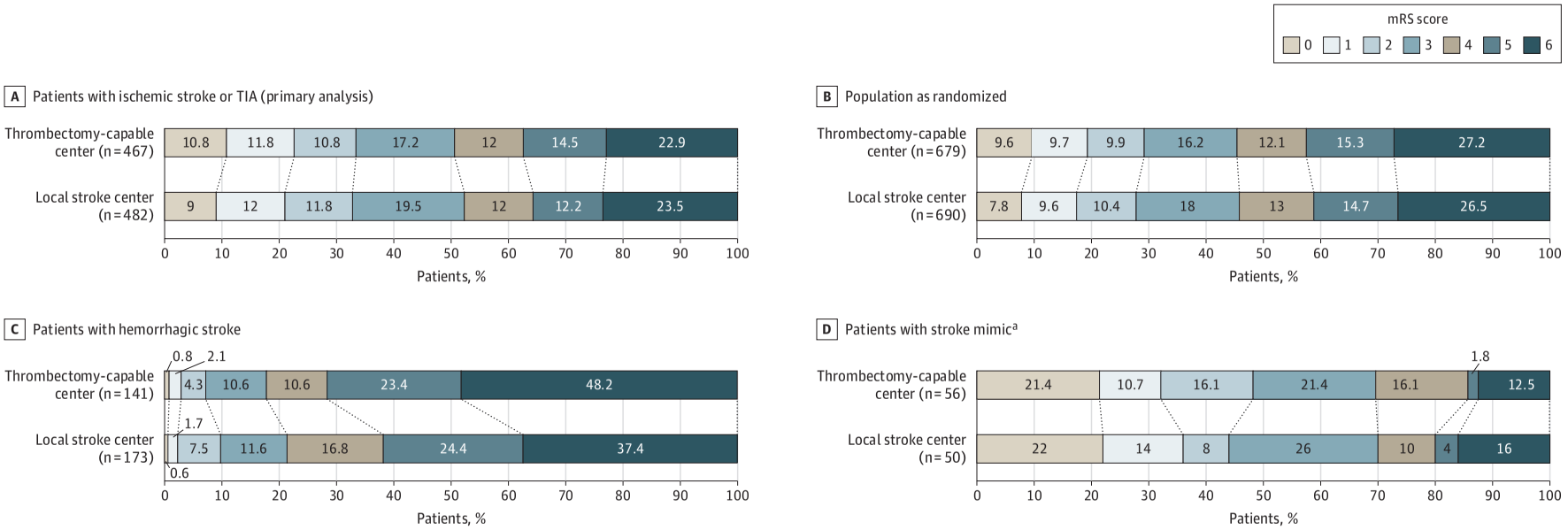
Overall, 920 patients (67.2%) with ischemic stroke, 29 patients (2.1%) with transient ischemic attacks or averted strokes, 314 patients (22.9%) with intracranial hemorrhage, and 106 patients (7.7%) with stroke mimic were included. Emergency medical services initial transport was performed by ground travel via ambulance in more than 99% of cases. Baseline demographic characteristics were similar between intervention groups (**Table 1**). Median times from allocation to first hospital arrival were 59 (IQR, 35-85) minutes and 22 (IQR, 14-33) minutes for thrombectomy-capable centers and local stroke centers, respectively. Median time from symptom onset to first hospital arrival was 140 (IQR, 99-216) minutes for the thrombectomy-capable center group and 91 (IQR, 64-155) for the local stroke center group.

Among the target population (949/1369 patients [69.3%]), 482 of 949 patients (51%) were allocated to thrombectomy-capable centers and 467 of 949 patients (49%) were allocated to local stroke centers; baseline characteristics were similar (Table 1). Vascular imaging during the acute phase was performed in at least 1 of the centers in 889 of 949 patients (94%); computed tomographic angiography was the vascular imaging type selected in most cases (>99%). Among patients who received vascular imaging at the first hospital, LVO was detected in 333 of 471 patients (71%) at thrombectomy-capable centers and in 198 of 260 patients (76%) at local stroke centers. Among patients first evaluated at a local stroke center, 302 patients (64.6%) were emergently transferred as thrombectomy candidates to a thrombectomy-capable center; the median door-in, door-out time at local stroke centers was 78 (IQR, 63-97) minutes.

Primary Outcome

Data on 90-day mRS scores were missing for 70 patients (5%) in the as-randomized population and in 33 patients (3%) in the target population. Among the target population, there was no significant difference among patients allocated to initial transport to a thrombectomy-capable center vs to a local stroke center in terms of global disability at 90 days, as indicated by the shift in the distribution of the mRS score

Figure 2. Distribution of Global Disability at 90 Days in Prespecified Populations

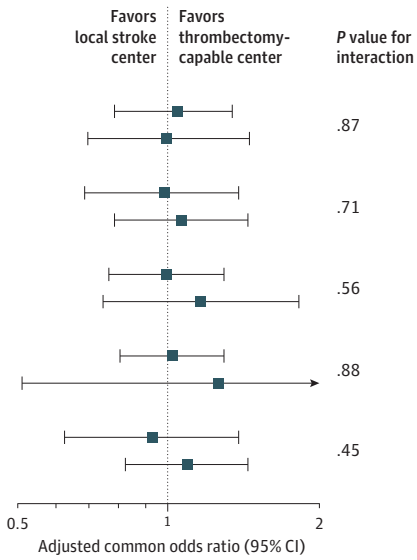


Distribution of modified Rankin Scale (mRS) scores at 90 days in prespecified subgroups of patients initially transported to a thrombectomy-capable stroke center vs a local stroke center who were evaluated by telephone interview with blinded investigators. See Figure 3 footnote *b* for description of mRS scores. Scores of 5 and 6 were combined for the analysis. Effects are reported below as common odds ratios (ORs) for better outcome, adjusted by stratifying factors, age, and Rapid Arterial Occlusion Evaluation (RACE) Scale score, for each specific population. The local stroke center group was the reference category. Data in the shaded boxes are percentage of patients. Panel A, Primary outcome in the target population, which includes patients with ischemic stroke or transient ischemic attack (TIA)/averted stroke (adjusted common OR, 1.03; 95% CI, 0.812-1.29). Panels B-D show secondary planned analyses. Panel B, Population as randomized (adjusted common OR, 1.05; 95% CI, 0.86-1.27). Panel C, patients with intracranial hemorrhage (adjusted common OR, 0.72; 95% CI, 0.44-1.18). Panel D, patients with stroke mimic (adjusted common OR, 0.90; 95% CI, 0.44-1.85).

[a] Final diagnoses for patients with stroke mimic included epileptic seizure (n = 39), functional disorder (n = 25), delirium (n = 9), subdural hemorrhage (n = 8), migraine (n = 7), intracranial tumor (n = 5), and cardiovascular syncope (n = 5). Diagnosis was not reported in 8 patients (7%).

Figure 3. Odds Ratios of a 1-Point Reduction in the Modified Rankin Scale (mRS) Score at 90 Days in Prespecified Subgroups

Subgroup	No./total No. (%) with 1-point reduction in mRS score at 90 d		Adjusted common odds ratio (95% CI)	*P* value for interaction
	Thrombectomy-capable center	Local stroke center		
Age, y				
<80	415/866 (48)	451/866 (52)	1.04 (0.78-1.34)	.87
≥80	264/503 (52)	239/503 (48)	0.99 (0.69-1.45)	
Sex				
Female	293/601 (49)	308/601 (51)	0.98 (0.68-1.38)	.71
Male	386/768 (51)	382/768 (49)	1.06 (0.78-1.44)	
tPA treatment eligibility[a]				
Yes	457/931 (49)	477/931 (51)	0.99 (0.76-1.29)	.56
No	222/435 (51)	213/435 (49)	1.16 (0.74-1.82)	
Confirmed mRS score 0-2 on hospital arrival[b]				
Yes	618/1254 (49)	636/1254 (51)	1.02 (0.80-1.29)	.88
No	61/114 (53)	53/114 (47)	1.26 (0.51-3.11)	
RACE Scale score during EMS evaluation[c]				
5-7	464/927 (50)	463/927 (50)	0.93 (0.62-1.38)	.45
8-9	215/442 (49)	227/442 (51)	1.08 (0.82-1.44)	



Effect sizes for the primary outcome of reduced disability (common odds ratio for 1-point reduction in mRS score) at 90 days, analyzed by ordinal logistic regression and adjusted for stratification factors, age, and Rapid Arterial Occlusion Evaluation (RACE) Scale score in prespecified subgroups by age, sex, baseline functional status, tissue plasminogen activator (tPA) treatment eligibility, and RACE Scale score during emergency medical services (EMS) evaluation.

[a] Patients were considered eligible for intravenous tPA administration at the time of randomization after evaluation by EMS personnel if the estimated travel time to the nearest stroke center was less than 4 hours and they received no anticoagulation treatment.

[b] Scores on the mRS range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help but able to walk unassisted; 4, moderately severe disability (unable to attend to bodily needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. Scores of 5 and 6 were combined for the analysis.

[c] RACE Scale scores range from 0 to 9 (lower to higher stroke severity, respectively). A score greater than 4 was the cut point to identify patients with a large-vessel occlusion and was considered the inclusion criterion.

(median mRS score, 3 [IQR, 2-5] in the thrombectomy-capable center group vs 3 [IQR, 2-5] in the local stroke center group; adjusted common OR, 1.03; 95% CI, 0.82-1.29) (**Figure 2**). Post hoc analyses performed using multiple imputation for missing outcomes and a mixed-effects model with clusters as random effects showed similar results (eTable 3 in Supplement 1).

Secondary Outcomes and Subgroup Analyses

Global disability at 90 days was not significantly different between intervention groups for the as-randomized population (median mRS score, 4 [IQR, 2-6] vs 4 [IQR, 2-6]; adjusted common OR, 1.05; 95% CI, 0.86-1.27) and for patients with intracranial hemorrhage (median mRS score, 5 [IQR, 4-6] vs 5 [IQR, 4-6]; adjusted common OR, 0.72; 95% CI, 0.44-1.18). In prespecified subgroup analysis for the primary outcome, no evidence of heterogeneity of treatment effect was found across the variables: age, sex, tPA eligibility, baseline mRS score, and RACE Scale score (**Figure 3**). Among the target population, 229 of 482 patients (47.5%) allocated to a thrombectomy-capable center received intravenous tPA, as did 282 of 467 patients (60.4%) allocated to a local stroke center (absolute difference, −12.9%; 95% CI, −19.2% to −6.6%; OR, 0.59; 95% CI, 0.45-0.76). In contrast, 235 of 482 patients (48.8%) allocated to a thrombectomy-capable center and 184 of 467 patients (39.4%) allocated to a local stroke center received thrombectomy (absolute difference, 10.1%; 95% CI, 3.8%-16.5%; OR, 1.46; 95% CI, 1.13-1.89). Median time from stroke onset to intravenous tPA administration was 155 (IQR, 120-195) minutes in the thrombectomy-capable center group and 120 (IQR, 89-168) minutes in the local stroke center group (median difference, 34.5 minutes; 95% CI, 22-45 minutes). Median time from stroke onset to thrombectomy initiation (groin puncture) was 214 (IQR, 172-330) minutes in the thrombectomy-capable center group and 270 (IQR, 215-347) minutes in the local stroke center group (median difference, −56 minutes; 95% CI, −72 to −29 minutes). Reasons for not performing thrombectomy and procedural information can be found in eTables 4 and 5 in Supplement 1. Other secondary outcomes are shown in **Table 2**.

The odds of better disability outcomes did not significantly differ according to estimated transport time to a thrombectomy-capable center (for each additional 30 minutes of estimated transport time, adjusted common ORs for worse outcome were 1.006 [95% CI, 0.808-1.253] in the thrombectomy-capable center group and 0.926 [95% CI, 0.772-1.110] in the local stroke center group; $P = .47$ for interaction). A post hoc analysis according to adapted American Heart Association recommendations for prehospital triage routing[10] is shown in eFigure 8 in Supplement 1.

Table 2. Primary and Secondary Efficacy Outcomes and Safety Outcomes[a]

Outcomes	Thrombectomy-capable center	Local stroke center	Absolute difference (95% CI)	Unadjusted OR or HR (95% CI)	Adjusted OR or HR (95% CI)
Primary efficacy outcome (target population)					
Modified Rankin Scale score at 90 d, median (IQR)	3 (2-5) [n = 482]	3 (2-5) [n = 467]		OR, 0.99 (0.78-1.24)	OR, 1.03 (0.82-1.29)
Secondary efficacy outcomes					
Modified Rankin Scale score at 90 d in as-randomized population, median (IQR)	4 (2-6) [n = 679]	4 (2-6) [n = 690]		OR, 1.00 (0.83-1.21)	OR, 1.05 (0.86-1.27)
Modified Rankin Scale score at 90 d in patients with intracranial hemorrhage, median (IQR)	5 (4-6) [n = 141]	5 (4-6) [n = 173]		OR, 0.67 (0.42-1.07)	OR, 0.72 (0.44-1.18)
Treatment with intravenous alteplase in target population, No./total (%)	229/482 (47.5)	282/467 (60.4)	−12.9 (−19.2 to −6.6)	OR, 0.59 (0.45-0.70)	
Treatment with thrombectomy in target population, No./total (%)	235/482 (48.8)	184/467 (39.4)	10.1 (3.8 to 16.5)	OR, 1.46 (1.13-1.89)	
Time from symptom onset to intravenous alteplase administration in target population, median (IQR), min[b]	155 (120-195)	120 (89-168)	34.5 (22 to 45)		
Time from symptom onset to groin puncture in target population, median (IQR), min[b]	214 (172-330)	270 (215-347)	−56 (−72 to −29)		
Dramatic early favorable response in target population, No./total (%)[c]	115/482 (23.9)	134/467 (28.7)	−4.8 (−10.4 to 0.7)	OR, 0.77 (0.58-1.04)	OR, 0.76 (0.55-1.02)
Safety outcomes (safety population)[d]					
Mortality at 90 d, No./total (%)	188/688 (27.3)	194/713 (27.2)	0.1 (−0.4 to 0.4)	HR, 0.99 (0.81-1.22)	HR, 0.96 (0.78-1.18)
Mortality at 90 d in patients with intracranial hemorrhage, No./total (%)	69/142 (48.6)	72/182 (39.6)	7.2 (−3.7 to 18.3)	HR, 1.30 (0.92-1.82)	HR, 1.21 (0.86-1.70)
Clinical worsening requiring intubation during transfer, No./total (%)	7/688 (1.0)	5/713 (0.7)	0.3 (−0.6 to 1.2)	OR, 1.45 (0.46-4.61)	OR, 1.52 (0.49-4.77)
Clinical worsening at 24 h, No./total (%)[e]	208/688 (30.2)	217/713 (30.4)	0.2 (−0.4 to 0.5)	OR, 0.99 (0.78-1.24)	OR, 0.99 (0.79-1.23)

Abbreviations: HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

[a] The target population included patients with confirmed diagnosis of ischemic stroke or transient ischemic attack/averted stroke (n = 949). The as-randomized population included patients enrolled in the trial who provided deferred informed consent (n = 1369). The safety population included all patients enrolled in the trial (n = 1401).

[b] Median differences and 95% CIs between intervention groups were obtained using a bootstrapping method with 1000 replications.

[c] Dramatic early favorable response was defined as an NIHSS score of 0 to 2 or improvement of 8 points or more at 24 hours (−2/+12 hours).

[d] Because informed consent was obtained on arrival at the first hospital, safety outcomes were required to be reported for all patients by the ethics committee and national authorities (Agencia Española del Medicamento y Producto Sanitario) to ensure that there were no safety concerns including among patients in which informed consent was not obtained.

[e] Clinical worsening at 24 hours was defined as an increase in NIHSS score of 4 points or more at 24 hours (−2/+12 hours).

Safety Outcomes

Among the safety population, the mortality rate at 90 days was 188 of 688 (27.3%) in the thrombectomy-capable center group and 194 of 713 (27.2%) in the local stroke center group (adjusted hazard ratio, 0.97; 95% CI, 0.79-1.18). In patients with intracranial hemorrhage, the mortality rate among patients allocated to a thrombectomy-capable center was 69 of 142 (48.6%) and among patients allocated to a local stroke center was 72 of 182 (39.6%) (adjusted hazard ratio, 1.21; 95% CI, 0.86-1.70) (Figure 2 and Table 2; eFigure 9 in Supplement 1). Clinical deterioration requiring intubation during primary transport occurred in 7 patients (1%) allocated to a thrombectomy-capable center and in 5 patients (0.7%) allocated to a local stroke center. Additionally, 3 patients (0.4%) required intubation during secondary interhospital transfer to a thrombectomy-capable center. Clinical deterioration at 24 hours occurred in 208 of 688 patients (30.2%) allocated to a thrombectomy-capable center and in 217 of 713 patients (30.4%) allocated to a local stroke center. All secondary safety outcomes and adverse events are presented in eTable 6 in Supplement 1.

Discussion

In this randomized clinical trial conducted among patients with suspected severe acute stroke located in nonurban areas of Catalonia, direct transport to a thrombectomy-capable center compared with transport to the closest local stroke center did not result in improved neurological outcomes.

Results of this trial differ from findings of several nonrandomized studies[7,8] and are counter to the assumptions of benefit in favor of bypassing local stroke centers.[9,21] Previous studies compared a population whose primary referral center was a thrombectomy-capable center with a population living in remote areas referred from local stroke centers. To our

knowledge, this is the first randomized trial comparing both transport modalities in patients enrolled directly from the field in nonurban areas not covered by thrombectomy-capable centers. Moreover, previous studies included only patients receiving thrombectomy; in this trial patients were included in the field, where the decision of initial transport destination is made. As a result, the outcome of patients ultimately not receiving thrombectomy, some of them receiving only intravenous tPA at the nearest local stroke center, was also accounted for. In a similar way, the effect of potential denial of thrombolytic treatment due to an additional initial transport time in patients allocated to a thrombectomy-capable center was also evaluated.

Workflow metrics around intravenous tPA and thrombectomy noted in this trial reflect a high level of efficiency in evaluation and treatment of patients with acute stroke that has not been replicated by most other systems of stroke care.[22-25] Consequently, the observed rate of thrombectomy among patients with ischemic stroke in this trial was substantially high irrespective of initial transport destination.[26] Moreover, the door-to-puncture time at thrombectomy-capable centers was shorter in patients secondarily transferred from local stroke centers, reflecting an efficient flow of information between centers that allowed such time reduction. Because clinical outcomes are critically dependent on the speed of reperfusion,[6] the study findings may not be applicable in regions with substantially larger differences in time from stroke onset to endovascular treatment initiation between patients directly transported to a thrombectomy-capable center and those transferred from local stroke centers. Improving workflows at the first hospital and transfer times should be a priority for stroke care systems.[27]

The reported results support the RACE Scale[14,28] as a widely usable screening tool for prehospital selection of patients with suspected LVO. Nonetheless, communication between EMS personnel and a neurologist was mandatory before randomization, which could partially explain the high-quality performance of prehospital triage during the trial.[13] The subgroup analysis by RACE Scale score did not suggest effect modification, so it is unlikely that a higher RACE Scale cut point would help in the selection of patients who might benefit from direct transport to a thrombectomy-capable center; the question of whether more accurate and novel technological triage tools may boost the benefit of bypassing local stroke centers warrants further investigation.[29]

A strength of this study is that it encompassed virtually the entire eligible study population of a confined area with respect to health care access, including a uniform EMS care system with standardized stroke evaluation and transport protocols. Furthermore, all stroke care, including general medical care, intravenous thrombolysis, endovascular treatment, and rehabilitation, were carried out within a system of relatively few hospitals whose practice patterns are largely protocolized, and clinical outcomes were uniformly captured in a mandatory region-wide registry with little variation in outcomes between centers.[22]

Findings of this study may have implications for the design of prehospital systems of care for acute stroke. Because direct transport to a thrombectomy-capable center was found to be neither beneficial nor detrimental, the best transport paradigm involving patients with suspected acute stroke due to LVO may be defined by local factors such as achievable workflow metrics, established practice patterns, and availability of local resources, rather than following a "one size fits all" approach.

Limitations

This study has several limitations. First, the assigned hospital determination did not occur based on uniformly applied criteria, as people living in the nearest metropolitan area were always directly served by a thrombectomy-capable center. Thus, reported results apply only to patients initially evaluated by EMS personnel in areas assigned to local stroke centers, mostly located more than 30 minutes away from a thrombectomy-capable center. Therefore, this study cannot establish the estimated transport time differences between hospitals that might yield a beneficial direct transport approach. Second, results of this trial do not apply to patients identified more than 7 hours after onset of symptoms since these patients were not included in the study due to lack of evidence for acute interventions in prolonged time windows at the beginning of the study. Third, about 44% of the patients transported to local stroke centers did not receive vessel imaging at the first hospital, compared with 2.5% of patients who were primarily transported to a thrombectomy-capable center (Table 1). Therefore, analyses related to vessel status should be interpreted with caution. Fourth, this study may have been underpowered to detect differences or harm for some subgroups, so secondary outcome results should be interpreted as exploratory. Fifth, there was an error in the method of allocation for the first 350 patients, in which the predefined allocation list was not strictly followed, although it appears unlikely to have substantially biased the results of the study.

Conclusions

In nonurban areas in Catalonia, Spain, there was no significant difference in 90-day neurological outcomes between transportation to a local stroke center vs a thrombectomy-capable referral center in patients with suspected LVO stroke. These findings require replication in other settings.

ARTICLE INFORMATION

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Additional Contributions: Neus Roldan, BSc, and Alba Singla, BSc (CRO Anagram) provided logistical and administrative support and clinical data monitoring (compensated). Neus Cerdà, BSc, Mireia Bonet, BSc (Bioclever) provided interim and final statistical analysis (compensated). Guillem Gallofré (Catalan Stroke Program) provided data management and technical support for the data collection (compensated). The steering committee designed the study, reviewed analyses with study statisticians, and collaborated in writing the manuscript.

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