Workflow Times and Outcomes in Patients Triaged for a Suspected Severe Stroke

Álvaro García-Tornel, MD, PhD,[1] Laia Seró, MD,[2] Xabier Urra, MD, PhD,[3] Pere Cardona, MD,[4] Josep Zaragoza, MD,[5] Jerzy Krupinski, MD,[6] Manuel Gómez-Choco, MD, PhD,[7] Natalia Mas Sala, MD,[8] Esther Catena, MD,[9] Ernest Palomeras, MD,[10] Joaquin Serena, MD, PhD,[11] Maria Hernandez-Perez, MD, PhD,[12] Sandra Boned, MD, PhD,[1] Marta Olivé-Gadea, MD,[1] Manuel Requena, MD, PhD,[1,13] Marian Muchada, MD, PhD,[1] Alejandro Tomasello, MD,[13] Carlos A. Molina, MD, PhD,[1] Mercè Salvat-Plana, RN,[14] Mar Escudero, RN,[15] Xavier Jimenez, MD, PhD,[15] Antoni Davalos, MD, PhD,[12] Tudor G. Jovin, MD, PhD,[16] Francesc Purroy, MD, PhD,[17] Sonia Abilleira, MD, PhD,[14] Marc Ribo, MD, PhD,[1] and Natalia Perez de la Ossa, MD, PhD,[12] for the RACECAT trial investigators

Introduction: Current recommendations for regional stroke destination suggest that patients with severe acute stroke in non-urban areas should be triaged based on the estimated transport time to a referral thrombectomy-capable center.
Methods: We performed a post hoc analysis to evaluate the association of pre-hospital workflow times with neurological outcomes in patients included in the RACECAT trial. Workflow times evaluated were known or could be estimated before transport allocation. Primary outcome was the shift analysis on the modified Rankin score at 90 days.
Results: Among the 1,369 patients included, the median time from onset to emergency medical service (EMS) evaluation, the estimated transport time to a thrombectomy-capable center and local stroke center, and the estimated transfer time between centers were 65 minutes (interquartile ratio [IQR] = 43–138), 61 minutes (IQR = 36–80), 17 minutes (IQR = 9–27), and 62 minutes (IQR = 36–73), respectively. Longer time intervals from stroke onset to EMS evaluation were associated with higher odds of disability at 90 days in the local stroke center group (adjusted common odds ratio

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26489

Received May 5, 2022, and in revised form Jul 21, 2022. Accepted for publication Aug 18, 2022.

Address correspondence to Dr Marc Ribo, Unitat d'Ictus, Hospital Vall d'Hebron, Departament de Medicina, Universitat Autònoma de Barcelona, Passeig Vall d'Hebron 119-129, Barcelona, 08035, Spain. E-mail: marcriboj@gmail.com

From the [1]Stroke Unit, Department of Neurology, Hospital Universitari Vall d'Hebron, Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Department of Neurology, Hospital Universitari Joan XXIII, Tarragona, Spain; [3]Stroke Unit, Hospital Clínic, Barcelona, Spain; [4]Stroke Unit, Hospital Universitari Bellvitge, L'Hospitalet de Llobregat, Spain; [5]Department of Neurology, Hospital Verge de la Cinta, Tortosa, Spain; [6]Department of Neurology, Hospital Mútua Terrassa, Terrassa, Spain; [7]Department of Neurology, Complex Hospitalari Hospital Moisés Broggi, Sant Joan Despí, Spain; [8]Department of Neurology, Hospital Sant Joan de Déu - Fundació Althaia, Manresa, Spain; [9]Department of Neurology, Consorci Sanitari Alt Penedès-Garraf, Vilafranca del Penedès, Spain; [10]Department of Neurology, Hospital Mataró, Mataró, Spain; [11]Stroke Unit, Hospital Universitari Josep Trueta, Girona, Spain; [12]Stroke Unit, Hospital Germans Trias i Pujol, Badalona, Spain; [13]Department of Interventional Neuroradiology, Hospital Vall d'Hebron, Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [14]Stroke Program, Catalan Health Department, Agency for Health Quality and Assessment of Catalonia (AQuAS), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; [15]Sistema d'Emergències Mèdiques, Barcelona, Spain; [16]Neurological Institute, Cooper University Hospital, Camden, NJ; and [17]Stroke Unit, Department of Neurology, Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Spain

Additional supporting information can be found in the online version of this article.

(acOR) for each 30-minute increment = 1.03, 95% confidence interval [CI] = 1.01–1.06), with no association in the thrombectomy-capable center group (acOR for each 30-minute increment = 1.01, 95% CI = 0.98–1.01, $p_{interaction}$ = 0.021). No significant interaction was found for other pre-hospital workflow times. In patients evaluated by EMS later than 120 minutes after stroke onset, direct transport to a thrombectomy-capable center was associated with better disability outcomes (acOR = 1.49, 95% CI = 1.03–2.17).

Conclusion: We found a significant heterogeneity in the association between initial transport destination and neurological outcomes according to the elapse of time between the stroke onset and the EMS evaluation (ClinicalTrials.gov: NCT02795962).

ANN NEUROL 2022;92:931–942

Acute ischemic stroke is considered one of the most time-sensitive medical conditions.[1] Reperfusion treatments, including thrombolytic treatment and, for patients with confirmed large vessel occlusion (LVO), endovascular thrombectomy, have been demonstrated to increase the odds of good functional outcome.[2–4] Its strongly time-dependent benefit has led to the development of protocols to minimize delays on reperfusion treatment administration.[5–7] In the past years, raising interest has grown on acute stroke pre-hospital management due to the development and validation of different pre-hospital stroke scales[8,9] that could help identify patients with higher odds of suffering a stroke due to LVO by emergency medical services (EMS). The main rationale for its development was that an early identification of this population might aid in the decision-making process in patients whose primary referral center is not able to perform thrombectomy. Thrombectomy is generally performed in urban thrombectomy-capable stroke centers, as facilities and expertise needed are not available in most local stroke centers. Inversely, thrombolytic treatment is widely available in most local stroke centers, being administered in patients with an acute ischemic stroke before referral to a thrombectomy-capable center for evaluation, if deemed indicated.

The current dilemma is whether to transport a patient with a suspected acute severe stroke to the closest local stroke center, or to its referral thrombectomy-capable center, avoiding potential delays associated with inter-hospital transfers. RACECAT[10] was a cluster-randomized trial that did not find a significant difference in neurological outcomes between transportation to a thrombectomy-capable center versus the closest local stroke center, with no predefined subgroup in which one pre-hospital transport destination would be beneficial or detrimental. Clinical[11] and computational probability modeling[12] studies have suggested that the estimated transport time to a referral thrombectomy-capable center might constitute a useful indicator for acute stroke pre-hospital triage decision making. Although guidelines for acute stroke management recommend initial evaluation at the closest stroke center,[13] updated recommendations for regional stroke destination from different scientific societies endorse that patients with an acute severe stroke in non-urban areas should be triaged based on estimated transport time to a referral thrombectomy-capable center and relative transport times between centers.[14] In this post hoc analysis of the RACECAT trial, we aim to evaluate which pre-hospital workflow time was associated with neurological outcomes and could be able to optimize the triage decision making of patients to referral thrombectomy-capable centers.

Methods

Study Design

RACECAT was a spatial–temporal cluster-randomized trial that included patients with suspected stroke with high odds of harboring an LVO, as evaluated by a Rapid Arterial Stroke Evaluation (RACE) scale score[15] (ranging from 0 [no findings] to 9 [severe neurological impairment]) of 5 or more, in areas not covered by a thrombectomy-capable center in Catalonia. The trial evaluated the efficacy and safety of direct transport to a thrombectomy-capable center, bypassing the closest local stroke center. Evaluation was performed on-scene by paramedics: the patients had to be independent for activities of daily living (modified Rankin score [mRs] of 2 or less) and be able to arrive at its referral thrombectomy-capable center before 7 hours from stroke onset. Acute stroke care in Catalonia (total population of 7.5 million inhabitants) is provided through a network of 28 hospitals, including 6 thrombectomy-capable centers situated in the Barcelona metropolitan area; geographic areas where the referral stroke center does not offer thrombectomy include 3.85 million inhabitants. Assignment to one out of the 2 possible transport destinations was performed in real-time by a smartphone-based system with a predefined randomized temporal schedule with 12-hour timeslots (3:00 AM to 2:59 PM and 3:00 PM to 2:59 AM) and stratified by territory (metropolitan vs provincial area) and weekday (workday vs holiday). The trial was approved by a central ethics committee and by the research board at each participating center. Patients or their legal representatives provided written informed consent. Detailed trial

protocol and its main results have been published elsewhere.[16]

Time Epochs

For this post hoc analysis, variables of interest were pre-hospital workflow times that were available or could be estimated during evaluation by EMS before trial enrollment. Time from onset to EMS evaluation was considered the time epoch between stroke symptom onset and the time that patients were allocated to one of the 2 trial groups through the smartphone-based system. For patients with unknown onset time, the last time seen well was computed as the onset time. To calculate travel distances and compute estimated workflow times since transport allocation, a mapping application was developed using the Google Maps Distance Matrix Application Programming Interface traffic model parameter. For each patient, stroke onset location and referral local stroke center and thrombectomy-capable 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. Estimated times extracted for analysis were the following: estimated transport time to the closest local stroke center, estimated transport time to its referral thrombectomy-capable center, difference in transport time to both centers, and estimated transfer time between both centers. Computed estimated times were compared and validated using the observed real times according to the initial transport destination.

Outcomes

The primary outcome was the shift analysis on the mRs at 90 days (ranging from 0 [no symptoms] to 6 [death]). Secondary outcomes included the proportion of patients with good functional outcome at 90 days, defined as a mRs score of 2 or less at 90 days, the proportion of patients treated with thrombolytic administration and thrombectomy, and the time from onset to thrombolytic administration and thrombectomy initiation. Functional outcome was centrally evaluated through a structured telephone-based interview by certified assessors blinded to group assignment.

Statistical Analysis

For the analyses, patients were analyzed according to their randomization group. Continuous variables are displayed as mean and SD or median and interquartile range (IQR; if not normally distributed). Categorical variables are displayed by the number and frequencies. Between group differences were assessed using a $\chi 2$ test (for categorical variables) and Student t test or Mann–Whitney U test (for noncategorical variables with or without normal distribution, respectively). For each patient, estimated transport time to its primary local stroke center, its referral thrombectomy-capable center, and transfer time between centers were compared with real observed times according to allocated transport modality using Spearman rho correlation coefficient. Missing scores on the primary outcome (mRs at 90 days) were imputed using a fully conditional specification multiple imputation method with 10 iterations and trial group, age, gender, baseline mRs score, baseline National Institutes of Health Stroke Scale (NIHSS) score, presence of LVO, thrombectomy, thrombolytic administration, NIHSS at 5 days, mRs at 5 days, and time from onset to transport allocation as target variables for the imputation. For the primary outcome, which included the population as randomized, the hypothesis was tested on a mixed-effect ordinal logistic regression model, with clusters as random effects variables, to estimate the common odds ratio (cOR) and 95% confidence intervals (CIs) of the ordinal shift in the distribution of disability at 90 days over the range of mRs. We obtained adjusted effects for each pre-hospital workflow time (the time from the onset to the EMS evaluation, estimated transport time to thrombectomy-capable center and local stroke center, difference in transport time to both centers, and estimated interhospital transfer time) and trial group (local stroke center and thrombectomy-capable center). For models including both trial groups, a multiplicative interaction term between pre-hospital workflow time tested and transport allocation was also included. Thrombectomy-capable center group was considered as the reference category. A sensitivity analysis was performed in the subgroup of patients with an initial diagnosis of ischemic stroke or transient ischemic attack (TIA)/averted stroke and the subgroup of patients with hemorrhagic stroke and stroke mimic. For the secondary outcome that evaluated the proportion of patients with good functional outcome, a mixed-effects binary logistic regression model was fitted to estimate the OR and its 95% CI using the same covariates and interaction terms as in the primary efficacy models. For pre-hospital workflow times with a significant interaction according to the trial group, graphical representations of outcomes as a function of time holding other variables constant at their mean were visually assessed for hypothetical cutoff points in which one transport routing would be beneficial. Factors associated with the administration of thrombolytic treatment and thrombectomy were evaluated in a binary logistic regression model for each trial group in patients with a final diagnosis of ischemic stroke/TIA. For the local stroke center group, we included the time from onset to the EMS evaluation, estimated transport time to the closest local stroke center (for both models), and estimated

interhospital transfer time (for the thrombectomy model). For the thrombectomy-capable center group, we included time from EMS evaluation and estimated transport time to referral thrombectomy-capable center. The relative contribution of each pre-hospital workflow time with time from onset to reperfusion treatment administration for each trial group was estimated and represented in stacked bar plots. All regression analyses were adjusted by age, RACE score, and the day of the week (weekdays and holiday); we did not include geographic location (metropolitan and provincial), a stratifying factor during trial enrollment, to avoid multicollinearity with estimated transport times. Tests were performed with a 2-sided α level of 5%. Because of the potential for type 1 error due to multiple comparisons, findings should be interpreted as exploratory. Statistical analysis was performed using SPSS Statistics version 25 (IBM Corporation, Armonk, NY). Graphical output was obtained from R version 4.1 (R Foundation for Statistical Computing).

Results

Between March 2017 and June 2020, there were 1,401 patients enrolled in the RACECAT trial. After excluding 32 patients (2.3%) who denied informed consent, 1,369 patients (mean age = 73 years, [SD = 13]; 601 women [43.9%]; median RACE score 7 (IQR = 6 to 8)) were included in the population as randomized. Median time from onset to EMS evaluation was 65 minutes (IQR = 44 to 135), with 89 patients (6%) evaluated within 30 minutes and 630 patients (46%) evaluated within 60 minutes after stroke onset. Median estimated transport time to the local stroke center, thrombectomy-capable center, and transfer time between centers were 16 minutes (IQR = 9 to 27), 61 minutes (IQR = 36 to 80), and 62 minutes (IQR = 36 to 73), respectively. No differences in estimated transport times were present between trial groups (Table 1). Estimated transport times correlated with observed transport times to the first hospital admission for each trial group (local stroke center group rho = 0.68, $p < 0.001$, thrombectomy-capable center group rho = 0.82, $p < 0.001$) and interhospital transfers rho = 0.70, $p < 0.001$; Fig 1).

Primary Outcome

Of 1,369 patients included in the primary outcome analysis, 690 patients (51%) were transported to a local stroke center and 679 (49%) patients were transported to a thrombectomy-capable center. Final diagnosis was ischemic stroke or TIA/averted stroke in 949 patients (69.3%, with 636 [67.3%] patients with an LVO diagnosed on vascular imaging). Among patients transported to a local stroke center, a longer time interval from onset to EMS evaluation was associated with higher degrees of disability at 90 days (for each 30-minute increment, adjusted common odds ratio [acOR] = 1.03, 95% CI = 1.01 to 1.06). In contrast, among patients directly transported to a thrombectomy-capable center, the time from onset to EMS evaluation was not associated with disability at 90 days (for each 30-minute increment, acOR = 1.00, 95% CI = 0.98 to 1.02, $p_{interaction} = 0.02$; Fig 2). We did not observe a significant interaction according to the estimated transport time to the local stroke center ($p_{interaction} = 0.43$), thrombectomy-capable center ($p_{interaction} = 0.43$), difference in transport time to both centers ($p_{interaction} = 0.66$), or interhospital transfer time

TABLE 1. Estimated and Observed Transport Times According to Transport Allocation

	Local stroke center (n = 690)	Thrombectomy-capable center (n = 679)
Onset to EMS evaluation, median (IQR)	63 (42–130)	67 (44–146)
Estimated time to thrombectomy-capable center, median (IQR)	61 (37–81)	62 (35–81)
Estimated time to local stroke center, median (IQR)	17 (9–28)	16 (9–27)
Difference in transport time to both centers, median (IQR)	38 (18–57)	36 (18–58)
Observed time to first hospital arrival, median (IQR)	22 (14–33)	59 (35–85)
Estimated transfer time between centers, median (IQR)	62 (36–73)	62 (36–73)
Observed transfer time between centers, median (IQR)	48 (31–71)	

Estimated transport times were computed using Google Maps Distance Matrix Application Programming Interface traffic model parameter.
Abbreviations: EMS = emergency medical services; IQR = interquartile ratio.

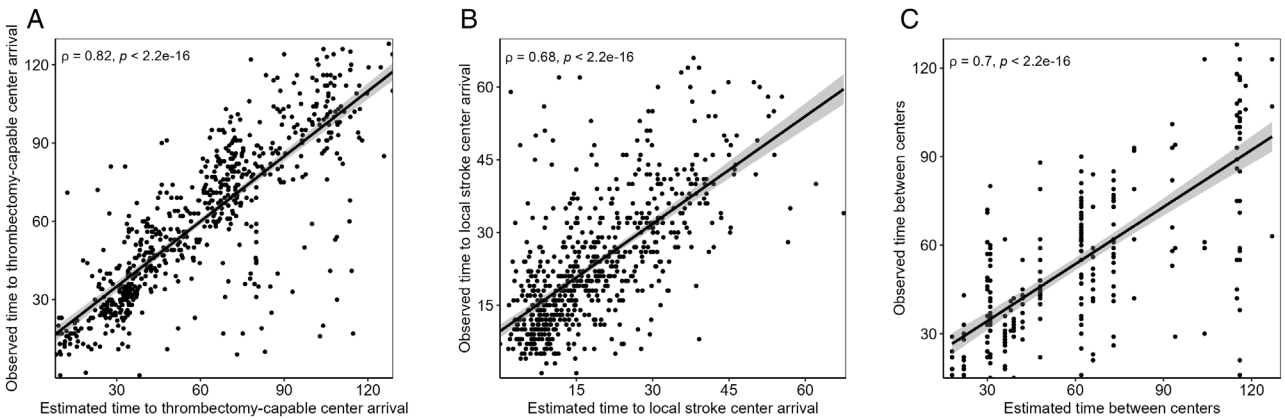

FIGURE 1: Correlation between estimated and observed transport times. Legend: Scatterplot showing the correlation, based on the Spearman rho coefficient, between estimated transport time to referral thrombectomy-capable center (thrombectomy-capable center group), (A) estimated transport time to closest local stroke center (local stroke center group), (B) and estimated interhospital transfer time (transferred patients group) (C). EMS = emergency medical services.

($p_{interaction}$ = 0.27; Table 2). In the sensitivity analysis performed in patients with an initial diagnosis of ischemic stroke or TIA/averted stroke, a longer time interval from onset to EMS evaluation was associated with higher odds of disability at 90 days in patients allocated to a local stroke center (for each 30-minute increment, acOR = 1.04, 95% CI = 1.01 to 1.07), with no association in patients allocated to a thrombectomy-capable center (acOR = 1.00, 95% CI = 0.98 to 1.02, $p_{interaction}$ = 0.02; Table 3). In contrast, no evidence of interaction was present in the subgroup of patients with a diagnosis of hemorrhagic stroke and stroke mimic (n = 420 [31%], $p_{interaction}$ = 0.69; Fig 3).

Secondary Outcomes

In the secondary outcome that evaluated the rate of good functional outcome among the population as randomized, we observed a significant interaction according to the time from the stroke onset to EMS evaluation and trial group. Longer time intervals from the stroke onset to EMS evaluation were associated with lower odds of functional independence in patients transported to a local stroke center (for each 30-minute increment, aOR = 0.92, 97.5% CI = 0.86 to 0.98), with no association in patients transported to a thrombectomy-capable center (for each 30-minute increment, aOR = 0.99, 97.5% CI = 0.97 to 1.02, $p_{interaction}$ = 0.01). We did not observe a significant treatment effect heterogeneity according to the estimated transport to the local stroke center ($p_{interaction}$ = 0.96), thrombectomy-capable center ($p_{interaction}$ = 0.88), difference in transport time to both centers ($p_{interaction}$ = 0.89), or interhospital transfer time ($p_{interaction}$ = 0.79; see Table 2).

A cutoff point of 120 minutes was selected because it represented approximately the fourth quartile in the

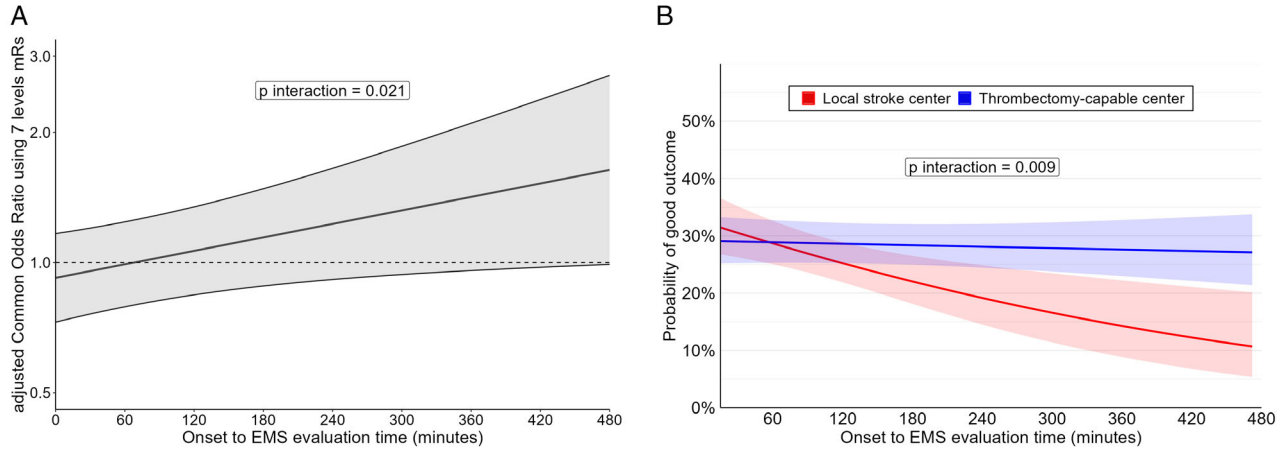

FIGURE 2: Primary and secondary outcomes in the population as randomized. Legend: Graphical representation of (A) primary outcome analysis (ordinal distribution of the mRs score at 90 days), and (B) secondary outcome analysis (proportion of patients with a mRs ≤2 at 90 days), as a function of time from onset to EMS evaluation. Primary outcome is represented as the odds ratio for a 1-level decrease in the mRs score at 90 days. Secondary outcome is represented as the probabilities of good functional outcome according to trial group. Models were adjusted for age, RACE score, and the day of the week. EMS = emergency medical services; mRs = modified Rankin score; RACE = Rapid Arterial Stroke Evaluation.

TABLE 2. Association between Pre-hospital Workflow Times and Outcome According to Initial Transport Destination in the Population as Randomized (n = 1,369)

		Primary outcome			Secondary outcome		
	Trial group	Adjusted cOR (95% CI)	*p* value	$p_{interaction}$	Adjusted OR (95% CI)	*p* value	$p_{interaction}$
Time from stroke onset to EMS evaluation	Local stroke center	1.034 (1.008–1.061)	0.011	0.019	0.915 (0.865–0.969	0.002	0.009
	Thrombectomy-capable center	1.003 (0.982–1.015)	0.839		0.994 (0.971–1.018)	0.611	
Estimated transport time to local stroke center	Local stroke center	0.939 (0.721–1.224)	0.643	0.429	0.979 (0.694–1.381)	0.979	0.479
	Thrombectomy-capable center	1.114 (0.834–1.486)	0.465		0.959 (0.662–1.388)	0.959	
Estimated transport time to thrombectomy-capable center	Local stroke center	0.942 (0.836–1.084)	0.460	0.434	0.956 (0.806–1.134)	0.605	0.379
	Thrombectomy-capable center	1.010 (0.889–1.147)	0.878		0.975 (0.825–1.152)	0.763	
Difference in estimated transport time to both centers	Local stroke center	0.998 (0.994–1.003)	0.494	0.666	1.001 (0.995–1.008)	0.643	0.895
	Thrombectomy-capable center	1.000 (0.995–1.004)	0.862		1.001 (0.995–1.007)	0.814	
Estimated interhospital transfer time	Local stroke center	0.895 (0.784–1.022)	0.101	0.272	1.011 (0.854–1.198)	0.895	0.354
	Thrombectomy-capable center	0.983 (0.865–1.117)	0.795		1.046 (0.888–1.234)	0.590	

Adjusted effect estimates for each pre-hospital workflow time and trial group in population as randomized are reported for the primary and secondary outcome that evaluated functional status at 90 days. Models were adjusted for age, RACE score, and the day of the week (weekdays and holidays). For the primary outcome, effects are expressed as the odds of a 1-level increment in the mRs at 90 days (worse outcome). For the secondary outcome, effects are expressed as the odds of good functional outcome at 90 days. Odds ratios are for each 30 minutes increment in the workflow time evaluated.

CI = confidence interval; cOR = corrected odds ratio; EMS = emergency medical services; mRs = modified Rankin score; OR = odds ratio; RACE = Rapid Arterial Stroke Evaluation.

distribution of time from the stroke onset to the EMS evaluation (n = 375 [27%], Table S1). In patients evaluated by EMS above 120 minutes after stroke onset, direct transport to a thrombectomy-capable center was associated with lower degrees of disability at 90 days (acOR = 1.50, 95% CI = 1.04 to 2.17) and higher odds of good functional outcome at 90 days (aOR = 1.67, 95% CI = 1.01 to 2.84). In contrast, among patients evaluated by EMS below 120 minutes after stroke onset (n = 991 [73%]), we did not observe a difference in global disability at 90 days (acOR = 0.96, 95% CI = 0.77 to 1.20) nor in the odds of good functional outcome at 90 days (aOR = 1.02, 95% CI = 0.77 to 1.35) according to trial group (Fig 4).

Patients with an ischemic stroke transported to local stroke centers had significant higher rates of thrombolytic treatment administration (282/467 [60.4%] vs 229/482 [47.5%]), but significantly lower rates of thrombectomy (192/467 [41.1%] vs 247/482 [51.2%]). Among patients with an ischemic stroke allocated to a local stroke center, longer time from onset to EMS evaluation was associated with a lower odds of thrombolytic treatment administration (for each 30-minute increment, aOR = 0.861, 95% CI = 0.811 to 0.913), with no significant association with the estimated transport time to the local stroke center (for each 30-minute increment, aOR = 1.015, 95% CI = 0.692 to 1.488). Among patients with an ischemic stroke allocated to a thrombectomy-capable center, longer

TABLE 3. Association Between Pre-hospital Workflow Times and the Primary Outcome According to Initial Transport Destination in Patients with Ischemic Stroke/TIA

	Trial group	Crude cOR (95% CI)	*p* value	Adjusted cOR (95% CI)	*p* value	$p_{interaction}$
Time from onset to EMS evaluation	Local stroke center	1.050 (1.021–1.080	0.001	1.040 (1.011–1.070)	0.007	0.021
	Thrombectomy-capable center	1.005 (0.988–1.023)	0.549	1.002 (0.985–1.020)	0.819	
Estimated transport time to local stroke center	Local stroke center	1.093 (0.802–1.488)	0.573	1.107 (0.809–1.514)	0.527	0.884
	Thrombectomy-capable center	1.064 (0.758–1.494)	0.721	1.084 (0.765–1.535)	0.651	
Estimated transport time to thrombectomy-capable center	Local stroke center	0.947 (0.810–1.107)	0.493	0.933 (0.797–1.092)	0.387	0.456
	Thrombectomy-capable center	1.014 (0.875–1.175)	0.851	0.989 (0.852–1.148)	0.885	
Difference in transport time to both centers	Local stroke center	0.997 (0.991–1.003)	0.284	0.996 (0.990–1.002)	0.174	0.369
	Thrombectomy-capable center	1.000 (0.995–1.005)	0.969	0.999 (0.994–1.004)	0.732	
Estimated interhospital transfer time	Local stroke center	0.888 (0.756–1.044)	0.150	0.873 (0.742–1.027)	0.101	0.321
	Thrombectomy-capable center	0.979 (0.845–1.134)	0.777	0.957 (0.825–1.111)	0.564	

Unadjusted and adjusted effects for each pre-hospital workflow time and trial group in the subgroup of patients with ischemic stroke / TIA (n = 949). Models were adjusted for age, Rapid Arterial Stroke Evaluation (RACE) scale score and the day of the week (weekdays and holidays). Effects are expressed as the odds as the odds of a 1-level increment in the mRs at 90 days (worse outcome) for each increment in 30 minutes in the workflow time interval evaluated.

CI = confidence interval; cOR = corrected odds ratio; EMS = emergency medical services; mRs = modified Rankin score; OR = odds ratio; TIA = trans ischemic attack.

time from the stroke onset to the EMS evaluation (for each 30-minute increment, aOR = 0.771, 95% CI = 0.713 to 0.835) and longer estimated transport time to a thrombectomy-capable center (for each 30-minute increment, aOR = 0.665, 95% CI = 0.547 to 0.809) were associated with a lower odds of thrombolytic treatment administration. No association was observed for any pre-hospital workflow time and the odds of receiving thrombectomy in both trial groups. The relative contribution of time from the stoke onset to the EMS evaluation on time to thrombolysis administration represented 51% (95% CI = 49% to 53%) in the local stroke center group and 42% (95% CI = 40% to 44%) in the thrombectomy-capable center group. For thrombectomy initiation, time from onset to EMS evaluation represented 27% (95% CI = 25% to 30%) and 39% (95% CI = 37% to 42%) of the time from the stoke onset to groin puncture in the local stroke center group and thrombectomy-capable center group, respectively (Fig 5).

Discussion

In this post hoc analysis of the RACECAT trial, we aimed to evaluate which pre-hospital workflow time available at the time of evaluation on-scene by EMS was able to help in the triage decision making in patients with a suspected large-vessel stroke. Main finding of our study is that the odds of better disability outcomes differed according to trial group and the time from the stroke onset to the EMS evaluation. Patients with a longer time interval from the stroke onset to the EMS evaluation had better neurological outcome if they were initially transported to a

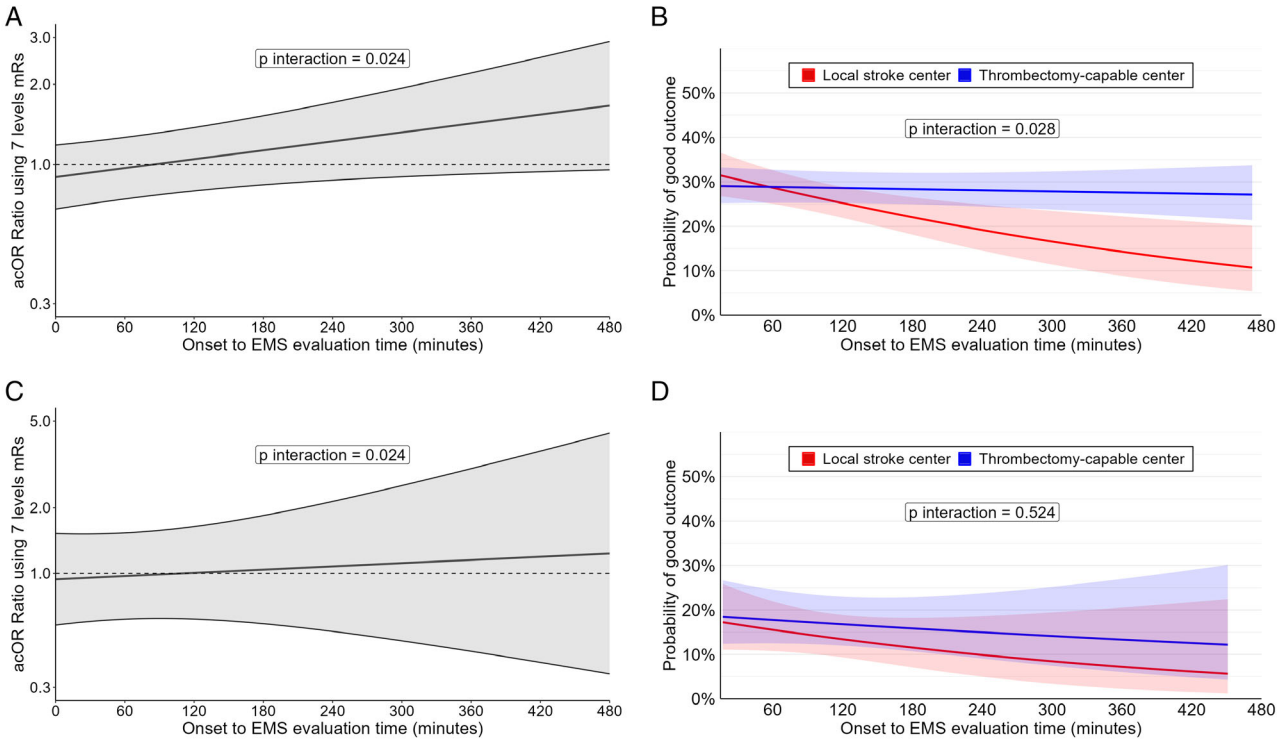

FIGURE 3: Primary and secondary outcomes according to stroke subtype. Legend: Graphical representation of primary and secondary outcome analysis according to trial group and stroke subtype as a function of time from onset to EMS evaluation. Treatment effect heterogeneity was only present for both outcomes in the subgroup of patients with an ischemic stroke/TIA (A, B), with no evidence of heterogeneity for other patients (C, D). Models were adjusted for age, RACE score, and the day of the week. acOR = adjusted common odds ratio; EMS = emergency medical services; RACE = Rapid Arterial Stroke Evaluation; TIA = transient ischemic attack.

thrombectomy-capable center. In patients evaluated by EMS above 120 minutes after stroke onset, there was a 34% relative increase in the odds of better disability outcomes if they were allocated to a thrombectomy-capable center, although they represented only about 25% of all included patients. The observed association among all patients was only present in patients with an ischemic stroke, with no association for other stroke subtypes (hemorrhagic stroke and stroke mimics). Estimated prehospital workflow times based on absolute or relative distances between patients, closest local stroke center, and its referral thrombectomy-capable center were not associated with neurological outcomes in this cohort. Furthermore, the odds of receiving thrombolytic treatment were mainly dependent on the time delay from the stroke onset to the EMS evaluation in both trial groups. As the rationale to

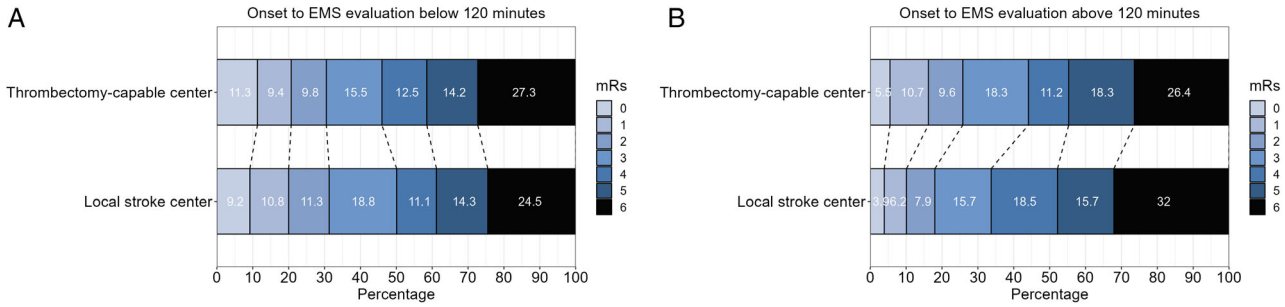

FIGURE 4: Distribution of global disability at 90 days according to time from onset to EMS evaluation with a cutoff point of 120 minutes. Legend: Stacked bar-plots which shows the distribution on the mRs scale at 90 days according to the time from stroke onset to the EMS evaluation selecting a cutoff point of 120 minutes. The common odds ratio for a better outcome at 90 days in patients allocated to a thrombectomy-capable center was 0.966 (95% CI = 0.774 to 1.205) and 1.503 (95% CI = 1.042 to 2.168) for patients evaluated by EMS below 120 minutes (n = 991 [73%], (A) and above 120 minutes (n = 375 [27%], and (B) after stroke onset, respectively. CI = confidence interval; EMS = emergency medical services; mRs = modified Rankin score.

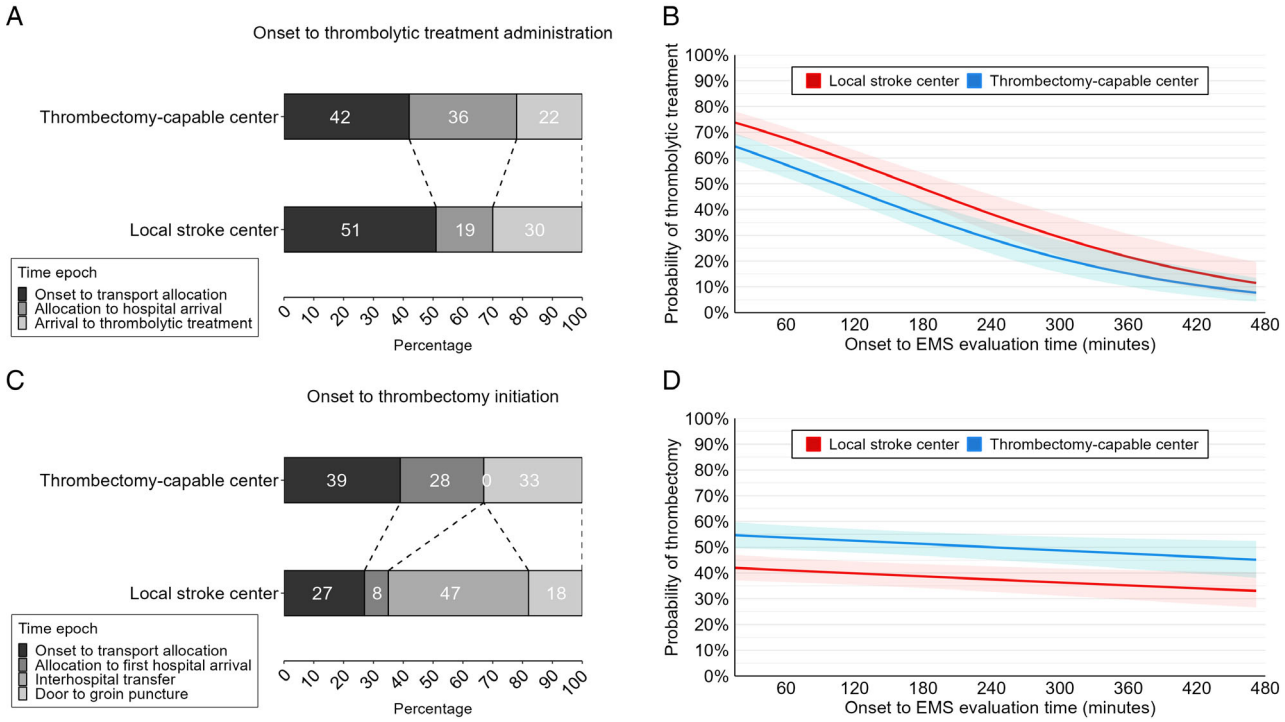

FIGURE 5: Contribution of different pre-hospital workflow times in reperfusion treatment administration. Legend: The contribution of each pre-hospital workflow time in the delay to thrombolytic treatment administration (A) and thrombectomy initiation (C) are represented as a percentage of time from onset to reperfusion treatment. The odds of thrombolytic treatment administration (B) and thrombectomy (D), estimated in a binary logistic regression model adjusted for confounding factors, according to trial group and as a function of time from onset to EMS evaluation. EMS = emergency medical services.

transport a patient with a suspected large-vessel stroke to closest local stroke center is to hasten thrombolytic administration,[17] a lower odds of thrombolytic treatment administration and a lower efficacy of thrombolytic treatment in patients with more delayed administration[3] could be considered for bypassing the local stroke center to avoid the potential delay associated with interhospital transfers.[11] In contrast, in patients evaluated earlier after stroke onset, a higher odd of receiving thrombolytic treatment and the greater clinical benefit of its administration supports that a drip-and-ship model for this population is comparable in terms of neurological outcomes as direct routing to a thrombectomy-capable center, bypassing the closest local stroke center. Moreover, patients with hemorrhagic stroke with a long time from the stroke onset to the EMS evaluation tend to be less severely affected and may therefore suffer less harm by long transport times to a thrombectomy-capable center.

The phrase "time is brain" emphasizes the rate of human nervous tissue loss as a function of time in patients with an acute ischemic stroke.[1] Its importance is further enhanced when it comes to reperfusion treatments: time to treatment has been demonstrated to be one of the most powerful modifiable prognostic factors in patients with an acute ischemic stroke. In the context of pre-hospital triage, the situation becomes extremely complex,[17] as the decision to choose one transport destination over the other may unwittingly decrease the patient's odds of good functional outcome.[18] Patients with a non-large-vessel ischemic stroke (34% of enrolled ischemic strokes in our cohort) would benefit from fast thrombolytic treatment in the closest local stroke centers.[19,20] Conversely, direct transportation of patients with an LVO to a thrombectomy-capable center would shorten the time to thrombectomy initiation,[11,21] although approximately 10% to 20% of them could have achieved early thrombolytic-related reperfusion if they had been initially transported to a local stroke center.[22,23] Moreover, it has been reported that the odds of thrombolytic-related reperfusion in patients with confirmed LVO is lower as the time from the stroke onset to its administration increases,[24] supporting a greater net benefit for patients with an ischemic stroke when they are evaluated in the ultra-early phase after the stroke onset.

Previous studies sought to predict the best initial transport destination in patients with an acute stroke,[12,25] balancing the benefits of early thrombolytic administration in local stroke centers with the greater efficacy of thrombectomy in patients with LVO directly admitted to a thrombectomy-capable center. Nonetheless, these

models were built making several assumptions related to thrombolytic and thrombectomy treatment eligibility and efficacy, and time model components, including time from onset to EMS evaluation, in order to estimate the odds of good functional outcome according to the initial transport destination. Differences between theoretical model assumptions and real-world care conditions can potentially bias the resulting model, overfitting predictions to conditions that do not represent real-world care. Our data suggests that, in contrast with current belief, and taking into account that RACECAT results may not be generalizable to other stroke systems of care, the most important pre-hospital workflow time during the trial was the time epoch from the stroke onset to the EMS evaluation, as the longer the delay to EMS evaluation the lower the odds of better disability outcomes for patients initially managed at local stroke centers.

Our results highlight the importance of stroke symptoms awareness and a fast EMS notification in order to facilitate a prompt hospital delivery for reperfusion treatment evaluation.[26–28] Although much effort in stroke systems of care has been devoted to reducing in-hospital workflow times, these efforts are diminished by the minimal improvements in pre-hospital delays in the past decades.[29] Time to EMS notification and evaluation comprises a significant proportion of the time until reperfusion treatment is administered, especially for the administration of thrombolytic treatment; interventions that aim to shorten the delay until the stroke code chain is activated by EMS could have a meaningful impact on the patient's prognosis worldwide.[30–32] Mobile stroke units' implementation could be a potential solution in some cases, as the time to thrombolytic administration would be shortened and the presence of an LVO could be confirmed on route to the thrombectomy-capable center.[33] Nonetheless, its associated costs and its feasibility in some geographic areas (mainly rural) should be further evaluated.

Our study emphasizes that in order to detect flaws for each specific stroke care system of care, and to find potential solutions, a real time evaluation of different stroke care continuum performance metrics should be reinforced to assure health care quality. It is crucial to analyze these data to allocate resources appropriately and recognize infrastructural weaknesses for each specific stroke health care system. Applicability of our results to other stroke systems of care might be limited. The Catalonian stroke system of care during trial enrollment period was centralized in Barcelona metropolitan area, where all thrombectomy-capable centers were located, with consistent rates of thrombolytic and thrombectomy treatment, little variations in workflow time metrics between centers,[34] and a unique provider of pre-hospital evaluation (Servei d'Emergències Mèdiques). As compared with other stroke systems of care in the United States, with a wide range of stroke center capabilities according to the Joint Commission,[35] larger variability in time metrics and annually patients volume across centers,[36,37] different locations and travel times between centers,[38] and different EMS providers rendering services in the same areas, direct application of our results should be cautiously considered.

Our study has several limitations. First, the post hoc analysis presented in this paper was not prespecified in the original trial protocol and is subject to inherent biases. Therefore, its conclusions should be cautiously taken and further validated. Second, study findings are highly dependent on its assumptions and the specific characteristics of the Catalonian stroke health care system. Real world care conditions might significantly vary across different countries and regions, thus the direct application of our findings outside Catalonia is limited. Third, computed estimated times had a moderate correlation to observed times in our cohort. Consequently, a more accurate tool to estimate transport times could have modified the results of our study. Fourth, the RACECAT trial included mainly patients with a short interval from stroke onset to EMS evaluation (median 65 minutes, IQR = 43–138), which were eligible for thrombolytic treatment. The inclusion of patients with more delayed evaluation, including wake-up strokes, should be evaluated for future trials.

Conclusion

In the RACECAT trial, we observed a significant heterogeneity in the association between the initial transport destination and the neurological outcomes according to the elapse of time between the stroke onset and the EMS evaluation, with more deleterious consequences of initial delays in patients transported to centers with no thrombectomy capabilities. Patients with delayed EMS evaluation had better neurological outcomes if they were initially transported to a thrombectomy-capable center. We did not find any significant association with other pre-hospital workflow times and outcomes. These findings need replication in other settings and geographies.

Acknowledgments

RACECAT trial was supported by Fundació Ictus Malaltia Vascular through an unrestricted grant from MEDTRONIC, by a grant from the Spanish Ministry of Health cofinanced by Fondo Europeo de Desarrollo Regional (Instituto de Salud Carlos III, Red Temática de Investigación Cooperativa RETICS-INVICTUS-PLUS RD0016/0019/0020), and from the PERIS programme

from the Catalan Health Government (project SLT008/18/0007).

Author Contributions

A.G.T., N.P.O., M.Ri., F.P., and S.A. contributed to the conception and design of the study. A.G.T., L.S., X.U., P.C., J.Z., J.K., M.G.C., J.S., M.H.P., S.B., M.O.G., M. Re., M.M., A.T., C.M., M.S.P., M.E., X.J., A.D., and T.J. contributed to the acquisition and analysis of data. A.G.T. drafted the manuscript and prepared the figures with significant contribution from N.P.O. and M.Ri.

Potential Conflicts of Interest

A.D. reports consultancy and advisory board fees from Medtronic Neurovascular (Steering Committee STAR), which funded the trial. T.J. received grants from Medtronic, which funded the trial. M.R. received grants and personal fees from Medtronic, which funded the trial. The other authors have no conflicts of interest to disclose.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Saver JL. Time is brain—quantified. Stroke 2006;37:263–266.
2. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA 2016;316:1279–1288.
3. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935.
4. Jahan R, Saver JL, Schwamm LH, et al. Association between time to treatment with endovascular reperfusion therapy and outcomes in patients with acute ischemic stroke treated in clinical practice. JAMA 2019;322:252–263.
5. McTaggart RA, Yaghi S, Cutting SM, et al. Association of a Primary Stroke Center Protocol for suspected stroke by large-vessel occlusion with efficiency of care and patient outcomes. JAMA Neurol 2017;74:793–800.
6. Perez de la Ossa N, Abilleira S, Dorado L, et al. Access to endovascular treatment in remote areas: analysis of the reperfusion treatment registry of Catalonia. Stroke 2016;47:1381–1384.
7. Menon BK, Xu H, Cox M, et al. Components and trends in door to treatment times for endovascular therapy in get with the guidelines-stroke hospitals. Circulation 2019;139:169–179.
8. Duvekot MHC, Venema E, Rozeman AD, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (PRESTO): a prospective observational study. Lancet Neurol 2021;20:213–221.
9. Fassbender K, Walter S, Grunwald IQ, et al. Prehospital stroke management in the thrombectomy era. Lancet Neurol 2020;19:601–610.
10. Abilleira S, Perez de la Ossa N, Jimenez X, et al. Transfer to the local stroke center versus direct transfer to endovascular Center of Acute Stroke Patients with suspected large vessel occlusion in the Catalan territory (RACECAT): study protocol of a cluster randomized within a cohort trial. Int J Stroke 2019;14:734–744.
11. Froehler MT, Saver JL, Zaidat OO, et al. Interhospital transfer before Thrombectomy is associated with delayed treatment and worse outcome in the STRATIS registry (systematic evaluation of patients treated with Neurothrombectomy devices for acute ischemic stroke). Circulation 2017;136:2311–2321.
12. Holodinsky JK, Williamson TS, Demchuk AM, et al. Modeling stroke patient transport for all patients with suspected large-vessel occlusion. JAMA Neurol 2018;75:1477–1486.
13. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early Management of Patients with Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–e110.
14. Jauch EC, Schwamm LH, Panagos PD, et al. Recommendations for Regional Stroke Destination Plans in Rural, Suburban, and Urban Communities From the Prehospital Stroke System of Care Consensus Conference: A Consensus Statement From the American Academy of Neurology, American Heart Association/American Stroke Association, American Society of Neuroradiology, National Association of EMS Physicians, National Association of State EMS Officials, Society of NeuroInterventional Surgery, and Society of Vascular and Interventional Neurology: Endorsed by the Neurocritical Care Society. Stroke 2021;52:e133–e152.
15. Perez de la Ossa N, Carrera D, Gorchs M, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. Stroke 2014;45:87–91.
16. Perez de la Ossa N, Abilleira S, Jovin T, et al. 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. JAMA 2022;327:1–13.
17. Caplan LR. Primary stroke centers vs comprehensive stroke centers with interventional capabilities: which is better for a patient with suspected stroke? JAMA Neurol 2017;74:504–506.
18. Venema E, Groot AE, Lingsma HF, et al. Effect of Interhospital transfer on endovascular treatment for acute ischemic stroke. Stroke 2019;50:923–930.
19. Gorelick PB. Primary and comprehensive stroke centers: history, value and certification criteria. J Stroke 2013;15:78–89.
20. Yeo LL, Paliwal P, Teoh HL, et al. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. JAMA Neurol 2013;70:353–358.
21. Goyal M, Jadhav AP, Bonafe A, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: results from the SWIFT PRIME randomized controlled trial. Radiology 2016;279:888–897.
22. Ribo M, Alvarez-Sabin J, Montaner J, et al. Temporal profile of recanalization after intravenous tissue plasminogen activator: selecting patients for rescue reperfusion techniques. Stroke 2006;37:1000–1004.
23. Goyal M, Almekhlafi M, Dippel DW, et al. Rapid Alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. Stroke 2019;50:645–651.
24. Muchada M, Rodriguez-Luna D, Pagola J, et al. Impact of time to treatment on tissue-type plasminogen activator-induced recanalization in acute ischemic stroke. Stroke 2014;45:2734–2738.
25. Xu Y, Parikh NS, Jiao B, et al. Decision analysis model for prehospital triage of patients with acute stroke. Stroke 2019;50:970–977.
26. Acker JE 3rd, Pancioli AM, Crocco TJ, et al. Implementation strategies for emergency medical services within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association expert panel on emergency medical services systems and the stroke council. Stroke 2007;38:3097–3115.

27. Adeoye O, Nystrom KV, Yavagal DR, et al. Recommendations for the establishment of stroke Systems of Care: a 2019 update. Stroke 2019;50:e187–e210.

28. Fassbender K, Balucani C, Walter S, et al. Streamlining of prehospital stroke management: the golden hour. Lancet Neurol 2013;12: 585–596.

29. Pulvers JN, Watson JDG. If time is brain where is the improvement in prehospital time after stroke? Front Neurol 2017;8:617.

30. Gu HQ, Rao ZZ, Yang X, et al. Use of emergency medical services and timely treatment among ischemic stroke. Stroke 2019;50:1013–1016.

31. Audebert H, Fassbender K, Hussain MS, et al. The PRE-hospital stroke treatment organization. Int J Stroke 2017;12:932–940.

32. Soto-Camara R, Gonzalez-Bernal J, Aguilar-Parra JM, et al. Factors related to prehospital time in caring for patients with stroke. Emergencias 2021;33:454–463.

33. Fassbender K, Grotta JC, Walter S, et al. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. Lancet Neurol 2017;16:227–237.

34. Ictus. PD. Newsletter CICAT. Stroke Code Registry Catalonia. https://app.powerbi.com/view?r=eyJrIjoiYmUwYmM5MjYtMWJlNy00NDdiLTljNGMtYzU5N2Y3MjFkYzU2IiwidCI6IjNiOTQyN2RjLWQzMGUtNDNiYy04YzA2LWZmNzI1MzY3NmZlYyIsImMiOjh9. https://app.powerbi.com/view?r=eyJrIjoiYmUwYmM5MjYtMWJlNy00NDdiLTljNGMtYzU5N2Y3MjFkYzU2IiwidCI6IjNiOTQyN2RjLWQzMGUtNDNiYy04YzA2LWZmNzI1MzY3NmZlYyIsImMiOjh9. Accessed October 6, 2021.

35. Mack WJ, Mocco J, Hirsch JA, et al. Thrombectomy stroke centers: the current threat to regionalizing stroke care. J Neurointerv Surg 2018;10:99–101.

36. Baker DW, Schmaltz S, Kolbusz K, et al. Differences in performance on quality measures for thrombectomy-capable stroke centers compared with comprehensive stroke centers in 2019 to 2020. Stroke 2022;e000302.

37. Waqas M, Tutino VM, Cappuzzo JM, et al. Stroke thrombectomy volume, rather than stroke center accreditation status of hospitals, is associated with mortality and discharge disposition. J Neurointerv Surg 2022.

38. Yu CY, Panagos PD, Kansagra AP. Travel time and distance for bypass and non-bypass routing of stroke patients in the USA. J Neurointerv Surg 2022;neurintsurg-2022-018787.