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Prospective, Multicenter, Controlled Trial of Mobile Stroke Units

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ABSTRACT

BACKGROUND

Mobile stroke units (MSUs) are ambulances with staff and a computed tomographic scanner that may enable faster treatment with tissue plasminogen activator (t-PA) than standard management by emergency medical services (EMS). Whether and how much MSUs alter outcomes has not been extensively studied.

METHODS

In an observational, prospective, multicenter, alternating-week trial, we assessed outcomes from MSU or EMS management within 4.5 hours after onset of acute stroke symptoms. The primary outcome was the score on the utility-weighted modified Rankin scale (range, 0 to 1, with higher scores indicating better outcomes according to a patient value system, derived from scores on the modified Rankin scale of 0 to 6, with higher scores indicating more disability). The main analysis involved dichotomized scores on the utility-weighted modified Rankin scale (≥0.91 or <0.91, approximating scores on the modified Rankin scale of ≤1 or >1) at 90 days in patients eligible for t-PA. Analyses were also performed in all enrolled patients.

RESULTS

We enrolled 1515 patients, of whom 1047 were eligible to receive t-PA; 617 received care by MSU and 430 by EMS. The median time from onset of stroke to administration of t-PA was 72 minutes in the MSU group and 108 minutes in the EMS group. Of patients eligible for t-PA, 97.1% in the MSU group received t-PA, as compared with 79.5% in the EMS group. The mean score on the utility-weighted modified Rankin scale at 90 days in patients eligible for t-PA was 0.72 in the MSU group and 0.66 in the EMS group (adjusted odds ratio for a score of ≥0.91, 2.43; 95% confidence interval [CI], 1.75 to 3.36; P<0.001). Among the patients eligible for t-PA, 55.0% in the MSU group and 44.4% in the EMS group had a score of 0 or 1 on the modified Rankin scale at 90 days. Among all enrolled patients, the mean score on the utility-weighted modified Rankin scale at discharge was 0.57 in the MSU group and 0.51 in the EMS group (adjusted odds ratio for a score of ≥0.91, 1.82; 95% CI, 1.39 to 2.37; P<0.001). Secondary clinical outcomes generally favored MSUs. Mortality at 90 days was 8.9% in the MSU group and 11.9% in the EMS group.

CONCLUSIONS

In patients with acute stroke who were eligible for t-PA, utility-weighted disability outcomes at 90 days were better with MSUs than with EMS. (Funded by the Patient-Centered Outcomes Research Institute; BEST-MSU ClinicalTrials.gov number, NCT02190500.)

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A Quick Take is available at NEJM.org

The standard care of patients with acute ischemic stroke includes arrival at the emergency department in an ambulance followed by administration of tissue plasminogen activator (t-PA) if specific criteria are met, including the absence of cerebral hemorrhage on noncontrast computed tomography (CT).[1-3] Selected patients with intracerebral large-vessel occlusion may subsequently receive endovascular thrombectomy (EVT).[4-7] Outcomes with t-PA and EVT are best with treatment as soon as possible after the onset of stroke, especially if t-PA can be delivered within the first hour after stroke onset.[8,9] Guidelines suggest organization of stroke systems of care to expedite delivery of thrombolytic and thrombectomy treatment.[1,10] A potential way to reduce the time from stroke onset to treatment is with mobile stroke units (MSUs), which are ambulances equipped with a CT scanner, point-of-care laboratory testing, and personnel trained to diagnose and treat patients with stroke in the ambulance, including administration of t-PA and triage for EVT. MSUs have the potential to increase the frequency and speed the delivery of t-PA treatment,[11-15] but whether and how much t-PA treatment in an MSU alters outcomes has not been extensively studied.

We conducted a prospective, multicenter, alternating-week, cluster-controlled trial to compare clinical outcomes in patients eligible for t-PA who received care from an MSU as compared with standard care by emergency medical services (EMS).[16] We hypothesized that, as compared with EMS, MSUs would reduce disability at 90 days after stroke.

Methods

Trial Design and Interventions

The Benefits of Stroke Treatment Delivered by a Mobile Stroke Unit Compared with Standard Management by Emergency Medical Services (BEST-MSU) trial began enrollment in August 2014 in Houston and added MSUs in six additional cities until the final patient was enrolled in August 2020. Patients were considered to be enrolled if they met screening criteria for t-PA treatment on MSU or EMS arrival at the scene, whether or not they became eligible for the primary outcome analysis. All sites collaborated with local EMS to treat patients according to the trial protocol. The protocol has been published[16] and is available with the full text of this article at NEJM.org. The trial was approved by the institutional review board at each site, and written informed consent was obtained from all patients or their representative. The trial monitoring committee met 10 times throughout the trial; these meetings included overseeing one prespecified interim analysis for safety, efficacy or futility, and process. The t-PA produced by a recombinant DNA method (Activase) was supplied at no cost to the trial by Genentech, but this company and no other commercial entity was involved in the trial design, conduct, analysis, or reporting.

Each MSU was staffed by one or two paramedics, a CT technologist, and a critical care nurse.[17] A vascular neurology specialist supervised management on board or remotely through telemedicine, which have been shown to be similar in accuracy and speed.[18,19] Enrollment into the two trial groups was based on prospective designation of alternating MSU or EMS weeks at each site from 8 a.m. to 6 p.m. Monday through Saturday at the Houston site (which enrolled the most patients), 8 a.m. to 5 p.m. Monday through Friday at four sites, 8 a.m. to 8 p.m. Thursday through Tuesday at two sites, and 7 a.m. to 7 p.m. Monday through Friday at one site. Data were not collected for stroke calls at other hours.

Because blinded enrollment of individual patients was not possible, we took the following measures to reduce the potential for ascertainment bias: enrollment of patients on both MSU and EMS weeks on the basis of assessment of the same clinical and laboratory criteria carried out on arrival of the MSU or EMS on the scene, later adjudication of eligibility for t-PA by a vascular neurologist who was unaware of the trial-group assignments and treatment, and blinded assessment of 90-day outcomes by a trained site investigator.

Patients with potential stroke within 4.5 hours after the onset of symptoms (defined as the time that the patient was last known to be well) were identified by a 911 dispatch center. The EMS and MSU teams were both alerted on MSU and EMS weeks. The criteria for enrollment in the trial were the same in the MSU and EMS groups as determined on the scene: examination features consistent with acute stroke that produced any degree of disability (with no formal cutoff according to the score on the National Institutes of Health Stroke Scale [NIHSS]), stroke onset

within the previous 4.5 hours, and no obvious guideline contraindications to the use of t-PA. Eligibility for t-PA was determined subsequently from review of records by a single vascular neurologist who was unaware of the trial-group assignments and whether the patient received t-PA.

On weeks in which an MSU was assigned, the MSU met an EMS team on the scene (both were dispatched), where the patient's history, blood glucose level, and neurologic and general physical condition were jointly evaluated by the two teams. The following steps were taken on the scene by the MSU: establishment of intravenous access, determination of the NIHSS score (range, 0 to 42, with higher scores indicating more neurologic deficits), noncontrast CT of the head, blood-pressure control, and, if criteria were met,[2] t-PA initial bolus and start of infusion. If a cerebral hemorrhage was detected by CT in the MSU group, the patient was considered to be ineligible for t-PA. At three sites, CT angiography could be performed by the MSU if large-vessel occlusion was suspected. Patients were then transported to the emergency department of the destination stroke center on the basis of local EMS triage criteria, the same as during EMS weeks, and the emergency department was notified.

On weeks in which EMS was assigned, an MSU nurse (but not the MSU) met the patient and EMS at the destination emergency department that had been prenotified by EMS. Without delaying emergency department intake, the MSU nurse obtained data from the EMS paramedics regarding the patient's history, blood glucose level, and the findings of the neurologic and general physical examination. The MSU nurse extrapolated the baseline NIHSS score (on the scene at the time of first contact) from the patient's NIHSS score measured on arrival at the emergency department, amended on the basis of input from the EMS medic to reflect the examination at the time of EMS arrival on the scene. After arrival at the emergency department, the hospital-based stroke team managed the care of the patient, including imaging and decisions regarding administration of t-PA, without input from the MSU nurse.

OUTCOMES

The primary outcome was the score on the utility-weighted modified Rankin scale[20-23] at 90 days in patients who were adjudicated to be eligible to receive t-PA on the basis of subsequent blinded review (described in the protocol). The main comparison was between MSU and EMS in patients who were eligible for t-PA, whether or not they received t-PA. The utility-weighted modified Rankin scale is a measure of disability that assigns values to each of the standard seven functional levels on the modified Rankin scale (range, 0 to 6, with 0 indicating no deficit and 6 indicating death) depending on the patients' value of that level of function. Using data from the current trial, we derived these patient-centered utility weights in our population by mapping patients' reported scores on the EuroQol Group 5-Dimension 5-Level questionnaire to their scores on the modified Rankin scale.[24] (Details on the derivation of utility weights are provided in the Supplementary Appendix, available at NEJM.org.) The range of scores on the utility-weighted modified Rankin scale is 0 to 1, with higher scores indicating better outcomes according to a patient value system as a continuous measure. A difference of 0.03 or more on this scale has been stated to reflect a clinically important effect.[22,25] A score on the utility-weighted modified Rankin scale of at least 0.91 is approximately equivalent to a score on the modified Rankin scale of 0 or 1, denoting no or minimal disability. All modified Rankin scale assessments at 90 days involved the use of a standardized questionnaire (Rankin Focused Assessment)[26] and were obtained by a trained investigator at each site who was unaware of the trial-group assignments. We implemented a protocol to reduce loss to follow-up and missing data.

Secondary outcomes were changes across the modified Rankin scale for all patients who were eligible for t-PA and all patients who received t-PA, a 30% reduction (improvement) from baseline to 24 hours in the NIHSS score,[27] the percentage of eligible patients treated with t-PA and EVT, and time metrics related to treatment times from stroke onset. In a post hoc analysis that included all enrolled patients, we examined scores on the utility-weighted modified Rankin scale and on the modified Rankin scale that were obtained at the time of hospital discharge by an investigator who was aware of the trial-group assignments. Safety outcomes included symptomatic intracerebral hemorrhage,[28] death, and the number of patients with symptoms that mimic stroke (stroke mimics) who were treated

with t-PA in each trial group on the basis of final diagnosis after hospital evaluation.

STATISTICAL ANALYSIS

With a sample size of 1038, a pooled standard deviation for the primary outcome of 0.385, and our pilot experience showing a numerical imbalance in MSU as compared with EMS enrollment and a potential loss to follow-up of 5%,[14] we estimated at least 80% power to detect a between-group difference of 0.07 points in the score on the utility-weighted modified Rankin scale[15] (details are provided in the Supplementary Appendix). Chi-square, Fisher's exact, and Wilcoxon rank-sum tests were used to evaluate baseline differences between the groups for categorical and continuous variables.

The primary analysis was of the score on the utility-weighted modified Rankin scale in the subgroup of patients adjudicated to be eligible for t-PA, whether or not they received t-PA. The prespecified plan was to use linear regression, adjusted for prestroke score on the utility-weighted modified Rankin scale, site, and covariates associated with scores on the modified Rankin scale (baseline NIHSS score, age, and previous transient ischemic attack [TIA] or stroke). Because the assumptions of the linear-regression model and proportional-odds assumptions were not met, the prespecified statistical plan was defaulted to use a prespecified binary logistic regression for dichotomized scores on the utility-weighted modified Rankin scale of at least 0.91 or less than 0.91 (equivalent to a score on the modified Rankin scale of ≤1 or >1, as summarized in Table S1 in the Supplementary Appendix). The between-group difference in the mean score on the utility-weighted modified Rankin scale and the 95% confidence interval were estimated with the use of a two-sample t-test. Logistic regression was used for the secondary outcome of a 30% reduction in the NIHSS score.[29-31] The statistical analysis plan is available with the protocol at NEJM.org.

Because trial-group assignments to MSU or EMS were not truly randomized, in a post hoc analysis we used propensity scores[32,33] to estimate the MSU group effect on all outcomes regarding scores on the utility-weighted modified Rankin scale, the modified Rankin scale, and the NIHSS. The individual propensities for enrollment in the MSU group as compared with the EMS group were estimated with the use of a multivariable logistic-regression model, with treatment group as the outcome variable and the covariates site, baseline NIHSS score, prestroke score on the modified Rankin scale, age, Black or non-Black race, sex, and dichotomized interval between the time that the patient was last known to be well and EMS or MSU arrival (>1 hour or ≤1 hour). Standardized mean differences were used to assess covariate balance before and after weighting (all standardized mean differences were <0.1). The predicted probabilities were used to calculate stabilized inverse-probability weights. The score on the utility-weighted modified Rankin scale at 90 days was described with the use of means and standard deviations and by fitting a univariate linear regression with outcome (score on the utility-weighted modified Rankin scale at 90 days), covariate MSU group, and inverse-probability weight according to the propensity score.

If the score on the modified Rankin scale at 90 days was missing but was ascertained retrospectively by telephone, that value was used as the 90-day value. This method had weighted kappa accuracies of 0.89 to 0.93 in a BEST-MSU substudy.[34] For the remaining missing outcomes, we used multiple imputation by chained equations and Rubin's rules for pooling among 10 imputed data sets.[35]

Subgroup analyses were conducted as in the primary models. The trial was not powered to analyze these subgroups, and no definite conclusions can be drawn from these data. Analyses involving all enrolled patients were added post hoc to assess the chances of postenrollment selection bias and to align the analysis with overall MSU as compared with EMS management with the outcomes of the score on the modified Rankin scale at discharge and the NIHSS score at 24 hours.

The interim analysis of the dichotomized scores on the utility-weighted modified Rankin scale at 90 days was conducted by means of a two-sample, two-sided test of proportions with the use of a Haybittle–Peto boundary (alpha spent, 0.001). This interim boundary was not crossed, and the final analysis used an alpha of 0.05. Prespecified sensitivity analyses included results without imputation and using published utility weights. No adjustments for multiple comparisons were made for secondary outcomes,

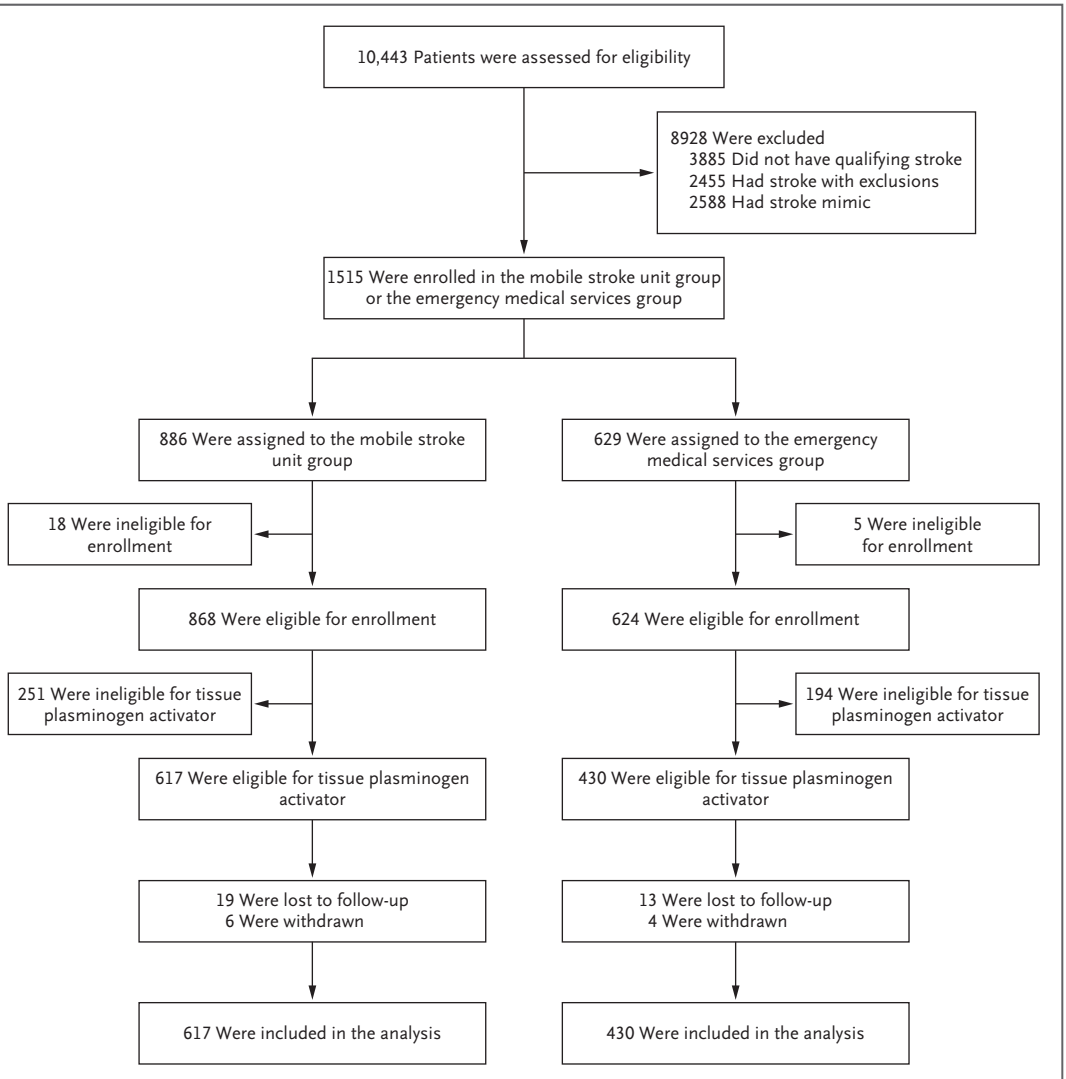

Figure 1. Screening, Randomization, and Follow-up.

and no conclusions can be drawn from these data. The analyses were performed with R software, version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

PATIENTS ENROLLED

From August 2014 to August 2020, we screened 10,443 emergency dispatches for MSU and EMS for stroke and enrolled 1515 patients, 886 (58.5%) in the MSU group and 629 (41.5%) in the EMS group. Of the 1515 enrolled patients, 617 patients (69.6%) in the MSU group and 430 patients (68.4%) in the EMS group (total, 1047) were adjudicated to be eligible for t-PA and were the population for primary analysis (Fig. 1 and Fig. S1). Of the patients who were eligible to receive t-PA, 97.1% who were assigned to MSU received t-PA, as compared with 79.5% in the EMS group (Table S2). Of the 1515 patients enrolled, 218 (14.4%) were not eligible for t-PA because intracranial blood was detected on CT.

Baseline characteristics were similar in the MSU and EMS groups for the patients eligible for t-PA, including stroke severity. Among all enrolled patients, the EMS group contained more men and more patients with a prestroke score on

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Patients Eligible for t-PA†		All Enrolled Patients	
	Mobile Stroke Unit (N=617)	Emergency Medical Services (N=430)	Mobile Stroke Unit (N=886)	Emergency Medical Services (N=629)
Median age (IQR) — yr	67 (57–79)	65 (55–78)	67 (55–78)	65 (55–77)
NIHSS score‡				
Median (IQR)	9 (5–16)	9 (6–16)	9 (5–17)	10 (6–16)
Distribution — no. (%)				
0–5	159 (25.8)	102 (23.7)	231 (26.1)	151 (24.0)
6–12	252 (40.8)	174 (40.5)	330 (37.2)	240 (38.2)
≥13	206 (33.4)	154 (35.8)	325 (36.7)	238 (37.8)
Sex — no. (%)				
Female	324 (52.5)	206 (47.9)	454 (51.2)	288 (45.8)
Male	293 (47.5)	224 (52.1)	432 (48.8)	341 (54.2)
Ethnic group — no. (%)§				
Hispanic or Latinx	97 (15.7)	80 (18.6)	145 (16.4)	132 (21.0)
Not Hispanic or Latinx	513 (83.1)	348 (80.9)	734 (82.8)	494 (78.5)
Not reported	7 (1.1)	2 (0.5)	7 (0.8)	3 (0.5)
Race or ethnic group — no. (%)§				
Asian	24 (3.9)	20 (4.7)	35 (4.0)	34 (5.4)
Black	241 (39.1)	172 (40.0)	344 (38.8)	245 (39.0)
White	338 (54.8)	224 (52.1)	487 (55.0)	336 (53.4)
Other	3 (0.5)	7 (1.6)	5 (0.6)	7 (1.1)
Not reported or unknown	11 (1.8)	7 (1.6)	15 (1.7)	7 (1.1)
Prestroke score on the modified Rankin scale — no. (%)¶				
0	379 (61.4)	288 (67.0)	526 (59.4)	415 (66.0)
1	79 (12.8)	47 (10.9)	118 (13.3)	66 (10.5)
2	57 (9.2)	21 (4.9)	84 (9.5)	38 (6.0)
3	74 (12.0)	58 (13.5)	113 (12.8)	84 (13.4)
4	27 (4.4)	16 (3.7)	42 (4.7)	25 (4.0)
5	1 (0.2)	0	3 (0.3)	1 (0.2)
Previous TIA or stroke — no. (%)				
No	427 (69.2)	293 (68.1)	600 (67.7)	425 (67.6)
Yes	186 (30.1)	136 (31.6)	279 (31.5)	201 (32.0)
Unknown	4 (0.6)	1 (0.2)	7 (0.8)	3 (0.5)
Site — no. (%)				
Houston	474 (76.8)	333 (77.4)	689 (77.8)	486 (77.3)
Colorado	69 (11.2)	31 (7.2)	108 (12.2)	51 (8.1)
Memphis, TN	30 (4.9)	24 (5.6)	40 (4.5)	34 (5.4)
New York	17 (2.8)	11 (2.6)	19 (2.1)	17 (2.7)
Los Angeles	6 (1.0)	17 (4.0)	8 (0.9)	25 (4.0)
Burlingame, CA	13 (2.1)	9 (2.1)	14 (1.6)	10 (1.6)

Table 1. (Continued.)

Characteristic	Patients Eligible for t-PA†		All Enrolled Patients	
	Mobile Stroke Unit (N=617)	Emergency Medical Services (N=430)	Mobile Stroke Unit (N=886)	Emergency Medical Services (N=629)
Indianapolis	8 (1.3)	5 (1.2)	8 (0.9)	6 (1.0)
Received t-PA within 4.5 hr after stroke onset — no. (%)‖	599 (97.1)	342 (79.5)	644 (72.7)	365 (58.0)

* Patients in the emergency medical services group received standard care. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and TIA transient ischemic attack.
† Eligibility for tissue plasminogen activator (t-PA) was determined by blinded adjudication.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more neurologic deficits.
§ Race and ethnic group were reported by the patient.
¶ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more disability (6 indicates death).
‖ Among the 599 t-PA–eligible patients in the MSU group who received t-PA, the bolus was delayed until after arrival at the emergency department in 12 patients; the remainder had t-PA started in the MSU. All the patients in the EMS group who received t-PA started treatment after arrival at the emergency department.

the modified Rankin scale of 0 (normal) than the MSU group (Table 1). Patients with stroke mimics represented approximately 9% of the patients eligible for t-PA in each group (Table S5). One trial site (Houston) enrolled 77.6% of the patients. A total of 35 patients received standard management by EMS during an MSU week; they were evaluated as part of the EMS group for the primary analysis and in the MSU group in a prespecified sensitivity analysis. Approximately 3% of the primary outcome data were missing in each group among patients eligible for t-PA.

PRIMARY OUTCOME

The mean (±SD) score on the utility-weighted modified Rankin scale at 90 days in the subgroup of patients eligible for t-PA was 0.72±0.35 in the MSU group and 0.66±0.36 in the EMS group (pooled difference, 0.07; 95% confidence interval [CI], 0.03 to 0.11; inverse-probability weighting–adjusted pooled difference, 0.08; 95% CI, 0.04 to 0.13) (Fig. S2). Among all 1515 enrolled patients, the mean score on the utility-weighted modified Rankin scale at discharge was 0.57±0.37 in the MSU group and 0.51±0.36 in the EMS group (pooled difference, 0.06; 95% CI, 0.03 to 0.10; inverse-probability weighting–adjusted pooled difference, 0.07; 95% CI, 0.03 to 0.11).

The primary analysis that used adjusted logistic regression for dichotomized 90-day scores on the utility-weighted modified Rankin scale of at least 0.91 or less than 0.91 (approximating a score on the modified Rankin scale of ≤1 or >1) resulted in a pooled odds ratio of 2.43 (95% CI, 1.75 to 3.36; P<0.001), favoring MSU in the models with or without inverse-probability weighting (Table 2 and Table S3). Excluding the 3.1% of patients lost to follow-up, the percentage of patients who were eligible for t-PA who had a score on the modified Rankin scale of 0 or 1 at 90 days was 55.0% in the MSU group and 44.4% in the EMS group (Fig. 2). The adjusted logistic-regression pooled odds ratio for a score on the utility-

Table 2. Distribution of Rankin Scores at 90 Days in Patients Eligible for t-PA.*

Score on Modified Rankin Scale (Equivalent Score on Utility-Weighted Modified Rankin Scale)	Mobile Stroke Unit (N=617)	Emergency Medical Services (N=430)
	number (percent)	
0 (1.00)	220 (35.7)	105 (24.4)
1 (0.91)	109 (17.7)	80 (18.6)
2 (0.74)	69 (11.2)	62 (14.4)
3 (0.65)	80 (13.0)	65 (15.1)
4 (0.19)	47 (7.6)	35 (8.1)
5 (0.03)	18 (2.9)	19 (4.4)
6 (0.00)	55 (8.9)	51 (11.9)
Missing or lost to follow-up	19 (3.1)	13 (3.0)

* Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more disability. Scores on the utility-weighted modified Rankin scale range from 0 to 1, with higher scores indicating better outcomes according to a patient value system. Percentages may not total 100 because of rounding.

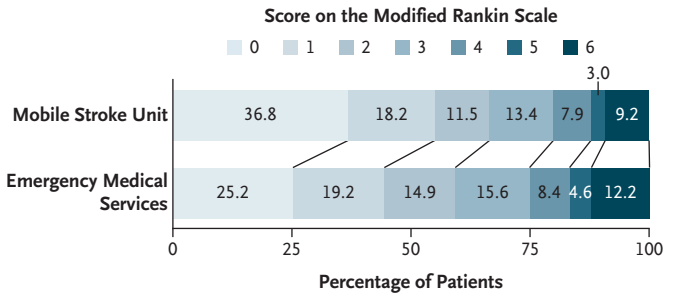

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days in Patients Eligible for t-PA.

Excluded were the approximately 3% of patients in each group who were lost to follow-up. Percentages may not total 100 because of rounding. The term t-PA denotes tissue plasminogen activator.

weighted modified Rankin scale of at least 0.91 at discharge in the total enrolled cohort was 1.82 (95% CI, 1.39 to 2.37; P<0.001) for the model with inverse-probability weighting and 1.84 (95% CI, 1.41 to 2.41) for the model without inverse-probability weighting (Table 2). The scores on the modified Rankin scale at discharge in all enrolled patients and in all enrolled patients excluding those with stroke mimics and cerebral hemorrhages are presented in Table S4.

SECONDARY OUTCOMES

A 30% reduction in the NIHSS score from baseline to 24 hours occurred in 75.0% of the patients eligible for t-PA in the MSU group and in 67.8% of those in the EMS group (adjusted odds ratio, 1.45 [95% CI, 1.09 to 1.91] with inverse-probability weighting and 1.45 [95% CI, 1.10 to 1.93] without inverse-probability weighting). Improvement to an NIHSS score of 0 by arrival at the emergency department occurred in 5.5% of the patients in the MSU group and in 3.3% of those in the EMS group with nonmissing data on the NIHSS score. The median time from stroke onset to t-PA treatment was 72 minutes in the MSU group and 108 minutes in the EMS group (Table 3); 32.9% of the patients in the MSU group and 2.6% of those in the EMS group were treated within 60 minutes after onset (Fig. S3). The median time from alerting of emergency services to EVT start was 141 minutes in the MSU group and 132 minutes in the EMS group, and the percentage of patients ultimately treated with EVT was 23.7% in the MSU group and 27.0% in the EMS group. Symptomatic intracerebral hemorrhages occurred in approximately 2% of the patients who received t-PA in each group and in none of the patients with stroke mimics. Mortality at 90 days was 8.9% in the MSU group and 11.9% in the EMS group.

Analysis of prespecified subgroups generally favored the MSUs for all patients who received t-PA, for Black and non-Black race, for time from stroke onset to EMS or MSU arrival within or after 1 hour, and across sites (Fig. S4); however, the trial was not powered to analyze these subgroups, and no definite conclusions can be drawn from these data. The correlation between time from stroke onset and ordinal score on the modified Rankin scale at 90 days and between treatment within the first hour after onset and a score on the modified Rankin scale of 0 or 1 at 90 days is shown in Figure S5.

The results of sensitivity analyses that used published[23] utility weights for the modified Rankin scale and that moved 35 patients from the EMS group who were enrolled during MSU weeks to the MSU group were consistent with the main results. A between-group comparison of the use of health care resources is being analyzed.

DISCUSSION

Our results show that in the areas served by the trial, patients who received emergency care within 4.5 hours after stroke onset had less disability on a utility-weighted scale at 90 days with MSU management than with management by EMS. The main analysis was restricted to patients who were qualified for treatment with t-PA as determined on review by an expert neurologist after assignment to the MSU group or EMS group. Patients were included at seven urban centers in the United States, had a wide range of stroke severity, were diverse (39.4% Black and 16.9% Hispanic), and included 24.3% with preexisting disability. The median time from onset of stroke to t-PA bolus in the EMS group was better than national benchmarks.[1,8] Treatment with t-PA was associated with symptomatic intracerebral hemorrhage in approximately 2% of the patients in each group. Similar outcomes have been reported in a study of MSUs that was conducted in Berlin.[36] We performed post hoc analyses of data for all

Table 3. Time Metrics in Patients Eligible for t-PA.*

Interval	Mobile Stroke Unit	Emergency Medical Services
	minutes	
Median interval between the time that the patient was last known to be well and t-PA treatment (IQR)	72 (55–105)	108 (84–147)
Median time from 911 alert to t-PA treatment (IQR)	46 (39–55)	78 (66–93)
Median time from ED door to t-PA bolus (IQR)	—	40 (30–51)
Median interval between the time that the patient was last known to be well and the alerting of emergency medical services (IQR)	23 (8–52)	22 (11–60)
Median time from 911 alert to arrival of emergency medical services (IQR)	9 (6–13)	9 (6–13)
Median time from arrival of emergency medical services to ED arrival (IQR)	55 (47–62)	27 (21–33)
Median interval between the time that the patient was last known to be well and endovascular thrombectomy (IQR)	166 (131–202)	163 (134–209)
Median time from 911 alert to endovascular thrombectomy (IQR)	141 (116–171)	132 (114–160)
Median time from ED door to endovascular thrombectomy (IQR)	76 (53–105)	94 (72–124)

* ED denotes emergency department.

transported (enrolled) patients, including those with stroke mimics and hemorrhages, and for all patients with ischemic stroke or TIA excluding those with stroke mimics and hemorrhages, and the results with MSU transport were generally in the same direction as those of the primary analysis.

Previous trials have shown that benefit from t-PA is greater with treatment within the first "golden hour" than at later times, yet an analysis conducted between 2009 and 2013[8] showed that only 1.3% of patients in U.S. stroke centers received t-PA within an hour after stroke onset. A total of 2.6% of the patients in our EMS group, as compared with 32.9% of those in the MSU group, received this treatment. It has been suggested that the pathophysiology of stroke is different in the first minutes after onset, that clots may be easier to lyse, and that brain tissue may have less irreversible injury than at later times after stroke onset.[37,38] Patients were more likely to receive t-PA in the MSU group than in the EMS group in our trial. This included both patients eligible for t-PA and those later adjudicated as not meeting standard criteria. Of patients who were not eligible for t-PA, 16.7% of those in the MSU group and 11.6% of those in the EMS group were treated with t-PA. Contributing to these differences is that 3.3% of the patients in the EMS group recovered to normal functioning by arrival at the emergency department, and others lost their chance for treatment by exceeding the time window of 4.5 hours. However, MSU management did not increase the frequency of or expedite EVT, although the time from arrival at an emergency department to the start of EVT was slightly shorter in the MSU group than in the EMS group. Obtaining CT angiography on the MSU in future trials may further reduce that time.[39]

A limitation of our trial is its nonrandomized design, which introduced the possibility of bias in group assignment. Analytic methods for observational trials were added post hoc, which affirmed the preplanned analyses. Randomization of individual patients was not possible because we could not withhold use of the MSU if it was available. Despite efforts to ensure comparable group assignments, there were differences in how the MSU and EMS groups were enrolled that might have introduced bias. First, on MSU weeks, a physician, nurse, and medic screened and enrolled patients and directly assessed the baseline NIHSS score on arrival on the scene. On EMS weeks, however, usually only the MSU nurse enrolled patients. Second, on EMS weeks, the EMS squad carried out a prehospital screening examination but not a full assessment of the NIHSS score. The baseline NIHSS score on those EMS

weeks was extrapolated on the basis of the score obtained by the MSU nurse and then amended on the basis of input from the EMS medic to reflect the examination at the time of EMS arrival on the scene. Third, there was a difference in how the MSU team was alerted on MSU weeks as compared with EMS weeks that led to an imbalance in the number of patients enrolled in each group. On MSU weeks, the team was alerted either by 911 dispatch or by the EMS squad if they arrived on the scene and discovered a stroke for which the MSU had not been dispatched. On EMS weeks, the MSU team was alerted by 911 dispatch as on MSU weeks but usually was not alerted by the EMS squad when they discovered a stroke for which the MSU had not been dispatched. Fourth, patients were adjudicated for eligibility for t-PA after trial-group assignments. Although the adjudicator for t-PA eligibility was unaware of the trial-group assignments, conclusions could be biased if data that were provided to the adjudicator influenced the decision regarding eligibility for t-PA.

Relatively few patients were enrolled at the six non-Houston sites, which limits the generalizability of our results. Enrollment at non-Houston sites was hampered by delayed start-up and the effects of the coronavirus disease 2019 pandemic. When the non-Houston sites were active, their enrollment was approximately 2.5 patients per month per site. The trial sites were primarily urban, and our results might be different in rural settings.

There were 10,448 possible stroke alerts resulting in 1047 patients eligible for t-PA in the trial, findings that suggest an opportunity to improve the efficiency of MSU and EMS dispatch. MSUs are costly and labor-intensive to implement and maintain, but they were considered to be cost-effective in modeling from an Australian study that used disability-adjusted life-years.[40] Alternatives to MSUs include ambulances that can triage patients through telemedicine but not treat them before arrival at the emergency department[41]; however, an effect of such ambulances on clinical outcomes has not been shown.

In this trial, MSU management of acute ischemic stroke in patients who were eligible to receive t-PA resulted in less disability at 90 days and faster and more frequent t-PA treatment than standard management by EMS.

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APPENDIX

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