Stroke

CLINICAL TRIAL

Beyond the Golden Hour: Treating Acute Stroke in the Platinum 30 Minutes

Anantbir S. Randhawa, MD*; Fatima Pariona-Vargas, MD*; Sidney Starkman, MD; Nerses Sanossian, MD; David S. Liebeskind, MD; Gilda Avila, MD; Samuel Stratton, MD; Jeffrey Gornbein, DrPH; Latisha Sharma, MD; Lucas Restrepo-Jimenez, MD; Miguel Valdes-Sueiras, MD; May Kim-Tenser, MD; Pablo Villablanca, MD; Robin Conwit, MD; Scott Hamilton, MD; Jeffrey L. Saver, MD

BACKGROUND: To emphasize treatment speed for time-sensitive conditions, emergency medicine has developed not only the concept of the golden hour, but also the platinum half-hour. Patients with acute stroke treated within the first half-hour of onset have not been previously characterized.

METHODS: In this cohort study, we analyzed patients enrolled in the FAST-MAG (Field Administration of Stroke Therapy–Magnesium) trial, testing paramedic prehospital start of neuroprotective agent ≤2 hours of onset. The features of all acute cerebral ischemia, and intracranial hemorrhage patients with treatment starting at ≤30 m of last known well were compared with later-treated patients.

RESULTS: Among 1680 patients, 203 (12.1%) received study agents within 30 minutes of last known well. Among platinum half-hour patients, median onset-to-treatment time was 28 minutes (interquartile range, 25–30), and final diagnoses were acute cerebral ischemia in 71.8% (ischemic stroke, 61.5%, TIA 10.3%); intracranial hemorrhage in 26.1%; and mimic in 2.5%. Clinical features among platinum half-hour patients were largely similar to later-treated patients and included age 69 (interquartile range, 57–79), 44.8% women, prehospital Los Angeles Motor Scale median 4 (3–5), and early-postarrival National Institutes of Health Stroke Scale deficit 8 (interquartile range, 3–18). Platinum half-hour acute cerebral ischemia patients did have more severe prehospital motor deficits and younger age; platinum half-hour intracranial hemorrhage patients had more severe motor deficits, were more often female, and less often of Hispanic ethnicity. Outcomes at 3 m in platinum half-hour patients were comparable to later-treated patients and included freedom-from-disability (modified Rankin Scale score, 0–1) in 35.5%, functional independence (modified Rankin Scale score, 0–2) in 53.2%, and mortality in 17.7%.

CONCLUSIONS: Prehospital initiation permits treatment start within the platinum half-hour after last known well in a substantial proportion of acute ischemic and hemorrhagic stroke patients, accounting for more than 1 in 10 enrolled in a multicenter trial. Hyperacute platinum half-hour patients were largely similar to later-treated patients and are an attainable target for treatment in prehospital stroke trials.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood pressure ■ cerebral hemorrhage ■ reperfusion ■ thrombectomy ■ transient ischemic attack

It is well-known that timely treatment in stroke is essential to improve patient functional outcomes.[1] For acute ischemic stroke, reperfusion therapy with intravenous thrombolysis and with endovascular thrombectomy are both highly time dependent and in preclinical models neuroprotective agents also show a strong time dependency.[2–5] For intracerebral hemorrhage, substantial clinical trial evidence suggests that blood pressure lowering

Correspondence to: Fatima Pariona-Vargas, MD, AV Atahualpa Km5, Cajamarca 06000, Peru. Email vargasfatima485@gmail.com
*Dr Randhawa and Dr Pariona-Vargas are joint first authors.
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Nonstandard Abbreviations and Acronyms

ACI	acute cerebral ischemia
FAST-MAG	Field Administration of Stroke Therapy–Magnesium
GCS	Glasgow Coma Scale
ICH	intracranial hemorrhage
IQR	interquartile range
LAMS	Los Angeles Motor Scale
mRS	modified Rankin Scale
OTT	onset to treatment

and start of prothrombotic agents are also beneficial in only a short time window and, within this window, the sooner the better for treatment start.[6,7]

Stroke is one of several emergency conditions in which patient outcome is heightened by accelerated treatment initiation; others include trauma, shock, status epilepticus, and cardiac arrest. To emphasize the importance of treatment speed for time-sensitive conditions, Emergency Medicine has developed several rubrics for different treatment time windows. The concept of the golden hour—the first 60 minutes after illness onset—is the most well-known,[8–10] but other useful time labels have also been promulgated. The terms platinum 30 minutes and platinum 10 minutes have been advanced for the most challenging and most beneficial time windows for intervention, when disease processes are least advanced and most reversible.[11–14]

For patients with stroke, sparse, but at least some, studies have delineated the clinical characteristics and treatment outcomes of golden hour patients. However, to our knowledge, the frequency, characteristics, and outcomes of platinum 30 minute patients has not been previously well characterized. These patients are generally not captured in studies of patients evaluated and treated in the Emergency Department. Even at the optimal attainable speed, the cumulative time intervals of symptom detection to 911 call (3–7 minutes), dispatcher phone assessment leading to ambulance activation (1–2 minutes), ambulance travel to scene (5–10 minutes), paramedic assessment and stabilization of patient and loading of patient into ambulance (10–20 minutes), ambulance travel from scene to Emergency Department door (5–10 minutes), and initial physician assessment in the ED (0–10 minutes) results in almost all patients with acute stroke arriving and assessed in the ED beyond the platinum 30 minutes.[15] Prehospital assessment and treatment is the only practical approach to achieving interventions for patients with stroke within the first 30 minutes after onset. Further, given the time needed to perform and review brain imaging, even Mobile Stroke Units are generally not able to achieve treatment times within the first 30 minutes.[16]

In contrast, standard ambulances staffed by paramedics are a widely available resource for potentially delivering stroke therapy in the platinum 30 minutes. However, patients with stroke assessed and treated by paramedics with neurovascular-targeted agents in the platinum 30 minutes have not been previously well-delineated. Understanding this population better is essential to the design of future trials focused upon the hyperacute period and to planning for implementation of trial-based treatments in practice. Accordingly, to achieve this objective, we analyzed this population in the National Institutes of Health FAST-MAG (Field Administration of Stroke Therapy—Magnesium) Phase 3 trial, a large, multicenter randomized trial assessing start of a potentially neuroprotective agent by paramedics in the field before hospital arrival.

METHODS

Data Availability

Anonymized data and materials have been made publicly available at the National Institute of Neurological Disorders and Stroke and can be accessed at www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets

Study Design

This cohort study is an exploratory analysis of the FAST-MAG trial, a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial which assessed magnesium sulfate initiated in the prehospital setting in patients with acute stroke within 2 hours of last known well time. The study database was originated and validated by an independent, outcome-blinded data collection and analysis team. The study was performed from January 2005 to March 2013 by a consortium including 40 emergency medical system agencies, 315 ambulances, 60 acute care receiving hospitals in Los Angeles and Orange counties in California. Details of study design and primary trial results have been presented in prior reports.[17–19] The study protocol was approved by the institutional review board at each emergency medical services agency and hospital study site. Enrollment occurred using explicit informed consent obtained via cellphone conversation between patients on the scene or their legally authorized representatives and enrolling physician-investigators off the scene or under exception from informed consent regulations.

At the first encounter in the prehospital setting, paramedics recorded vital signs, the severity of the stroke motor deficit on the Los Angeles Motor Scale (LAMS), level of consciousness on the Glasgow Coma Scale (GCS). After Emergency Department arrival, study coordinators assessed repeated vital sign, LAMS, and GCS assessments and also recorded multidomain neurological deficits on the National Institutes of Health Stroke Scale, demographics, past medical history, and medications taken before stroke onset.

The lead efficacy outcome at 3 months was nondisabled status/excellent outcome (modified Rankin Scale [mRS] score, 0–1). Secondary efficacy outcomes were functional independence (mRS score, 0–2) and the distribution of global disability

across all 7 mRS levels. All-cause mortality (mRS score, 6) was the lead safety end point. All mRS score assessments were performed by physician- and nurse-raters certified in the validated Rankin Focused Assessment method.

Patients were placed in time categories based on the time interval from last known well time to time of initiation of the prehospital study agent. Two analytic approaches were taken. In a granular analysis of time windows, patients were placed in 5 time categories: 15 to 30 minutes (platinum group); 31 to 45 minutes; 46 to 60 minutes; 61 to 120 minutes; and over 120 minutes. In a broad analysis of time windows, patients were placed in 2 categories: 15 to 30 minutes (platinum group) and >30 minutes. For the platinum group, the lower limit of 15 minutes was used because trial entry criteria required patient deficit to have lasted at least 15 minutes before enrollment.

Statistical Analysis

Descriptive statistics were used to characterize demographic, clinical, and outcomes characteristics of the study population. Numbers and percentages were used for binary variables and medians and interquartile ranges for continuous and ordinal variables. For scales with 15 or less levels, means and SDs are additionally reported. Three populations of patients were analyzed: (1) acute cerebral ischemia (ACI) patients, consisting of all patients with a final diagnosis of ischemic stroke or transient ischemic attack; (2) intracranial hemorrhage (ICH) patients; and (3) all enrolled patients, including ACI patients, ICH patients, neurovascular mimic patients, and patients unable to be classified combined.

Features distinguishing platinum half hour patients and later-treated patients were analyzed bivariately and using multivariable monitoring. The 17 baseline covariates analyzed were age, sex, race, Hispanic ethnicity, hypertension, diabetes, hyperlipidemia, atrial fibrillation, prior stroke or transient ischemic attack, tobacco use, alcohol use, motor deficit severity on the prehospital LAMS, laterality of prehospital LAMS motor weakness, level of consciousness on the GCS, time of day of onset, prehospital systolic blood pressure, and prehospital diastolic blood pressure. For the prehospital LAMS score, the lead analysis was nonparametric (median, interquartile range, Kruskal Wallis, and Mann Whitney) reflecting its ordinal character. However, as the LAMS scores had only 5 levels, limiting the informativeness of the median value in indicating group differences, for descriptive purposes the LAMS was also analyzed using parametric analysis (mean, SD, ANOVA, and *t* test), an approach appropriate for ordinal data in large sample sizes per the Central Limit Theorem.

In the bivariate analyses of platinum half hour patients versus all later-treated patients, Mann Whitney and χ^2 tests were used to compare patient groups, as appropriate. In the analyses comparing the 5 granular onset to treatment (OTT) groups (15–30 m, 31–45 m, 46–60 m, 61–120 m, >120 m), Kruskall Wallis tests were used for continuous outcomes. For dichotomized outcomes, χ^2 tests were used for binary predictor variables and Fisher Exact test for categorical predictor variables.

For the multivariable monitoring of features associated with platinum half-hour treatment, the 17 potential predictors were simultaneously assessed using logistic regression, classification tree (recursive partitioning) models and gradient boosting models. The boost analysis was used primarily to find nonlinear relationships and interactions among variables that could be used to refine the logistic model.[20] Model accuracy was summarized by the concordance (C) statistic; model performance was considered: excellent, 0.80 to 1.00; good, 0.70 to 0.79; fair, 0.60 to 0.69; and poor, 0.50 to 0.59.[21] Model accuracy was also summarized by the sensitivity, specificity, and overall accuracy.[21]

The relation of platinum half-hour treatment and treatment in later time epochs with functional outcomes was analyzed bivariately and multivariately, separately for acute cerebral ischemic patients and ICH patients, for 3 month end points of freedom-from-disability (mRS score, 0–1), functional independence (mRS score, 0–2), and mortality. Multivariate logistic regression modeling incorporated baseline features related bivariately to outcomes with $P<0.20$ plus platinum half-hour versus later treatment. In addition, OTT time as a continuous variable and the distribution of 3 month mRS outcomes in the ACI and in the ICH patients was analyzed using the Spearman correlation coefficient.

Two-tailed significance was considered at $P<0.05$. Statistical analysis was performed through SPSS, version27 (SPSS Inc).

RESULTS

Among the overall 1700 patients enrolled in the FAST-MAG Trial, 1680 (98.8%) had confirmed valid data for both last known well time and study agent prehospital start time. Final diagnosis among the patients was ACI in 1229 (73.15%, including acute ischemic stroke in 1028 [61.2%] and transient ischemic attack in 201 [12.0%]); ICH in 385 (22.9%); and neurovascular mimic in 64 (3.81%). Demographic and clinical characteristics of this all-patient population are presented in Text S1, Table S1, and Figure S1. Platinum half hour treatment occurred with comparable frequencies among ICH and ACI patients, 13.8% versus 11.7%; relative risk, 1.17 (95% CI, 0.88–1.58). Calls to EMS were placed earlier among platinum half-hour than later-treated patients, 5 (interquartile range [IQR], 2–6) versus 19 (IQR, 10–39), $P<0.001$.

Among the 1299 ACI patients, median age was 73 (IQR, 61–82), 44.5% were women, and prehospital LAMS was median 4 (IQR, 3–5; Table 1). The interval from last known well to study agent start was median 48 minutes (IQR, 36–68.8 minutes). The detailed distribution of onset-to-treatment times is shown in Figure 1A. The characteristics of patients in the binary categories of 1 to 30 minutes and >30 minutes and in each of the 5 more granular OTT categories are shown in Table 2. In the bivariate comparison of platinum half-hour treated patients versus later-treated patients, features strongly distinguishing the groups were age (lower in the platinum 30 minutes patients) and LAMS (more severe motor deficits in the platinum 30 minutes patients).

The results of multivariate models to distinguish platinum half hour patients from the later-treated patients among individuals with ACI are shown in Table S2. The multivariate additive logistic regression model incorporating all 17 baseline covariates to distinguish platinum half hour patients showed fair predictive accuracy, with

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Table 1. Descriptive Characteristics of Platinum Half-Hour and Later-Treated Acute Cerebral Ischemia Patients

	15–30 m (N=144)	31–45 m (N=424)	46–60 m (N=281)	61–120 m (N=336)	>120 m (N=44)	*P* value (comparing 5 groups)	>30 m (N=1085)	*P* value comparing 15–30 m and >30 m
Age, median (IQ) y	71 (59–80)	70.5 (59–81)	75 (62–83)	73 (62.3–81.8)	75 (65.3–85.8)	0.01*	73 (61–82)	0.03*
Sex, n (%)								
Female	59 (41.0)	182 (42.9)	135 (48.0)	153 (45.5)	24 (54.5)	0.38	494 (45.5)	0.34
Race, n (%)						0.71		0.48
White	115 (79.9)	326 (76.9)	221 (78.7)	26 (77.4)	33 (75.0)		840 (77.4)	
Black	19 (13.2)	52 (12.3)	41 (14.6)	51 (15.2)	7 (15.9)		151 (13.9)	
Asian	7 (4.9)	43 (10.1)	18 (6.4)	22 (6.6)	4 (9.1)		87 (8.0)	
Other	2 (1.4)	3 (0.7)	2 (0.7)	3 (0.9)	0 (0.0)		25 (2.3)	
Hispanic ethnicity, n (%)	25 (17.4)	78 (18.4)	60 (21.4)	76 (22.6)	9 (20.5)	0.57	223 (20.6)	0.39
Medical Hx, n (%)								
Hypertension	103 (71.5)	334 (78.8)	216 (76.9)	265 (78.9)	36 (81.9)	0.43	851 (78.4)	0.09*
Diabetes	32 (22.2)	80 (18.9)	66 (23.5)	91 (27.1)	14 (31.8)	0.06	251 (23.1)	0.84
Hyperlipidemia	78 (54.2)	201 (47.4)	140 (49.8)	181 (53.9)	22 (50.0)	0.39	544 (50.1)	0.32
Atrial fibrillation	42 (29.2)	113 (26.7)	85 (30.3)	80 (23.9)	11 (25.0)	0.45	289 (26.6)	0.48
Prior stroke/TIA	23 (16)	72 (17)	63 (22.4)	54 (16.1)	9 (20.5)	0.27	198 (18.3)	0.55
Tobacco use	18 (12.5)	82 (19.3)	45 (16.0)	60 (17.9)	11 (25.0)	0.23	198 (18.3)	0.095
Any alcohol use	53 (36.8)	171 (40.3)	88 (31.3)	127 (37.8)	16 (36.4)	0.19	402 (37.1)	0.99
LKWT, n (%)†						<0.001*		0.39
0001–0400	0 (0)	3 (0.7)	7 (2.5)	7 (2.1)	3 (6.8)	0.01*	20 (1.8)	0.16
0401–0800	6 (4.2)	15 (3.5)	20 (7.1)	32 (9.5)	9 (20.5)	<0.001*	76 (7)	0.21
0801–1200	40 (27.8)	113 (26.7)	71 (25.3)	94 (28.0)	8 (18.2)	0.66	286 (26.4)	0.65
1201–1600	42 (29.2)	114 (26.9)	73 (26.0)	81 (24.1)	6 (13.6)	0.26	274 (25.3)	0.27
1601–20:00	31 (21.5)	112 (26.4)	57 (20.3)	67 (19.9)	11 (25.0)	0.19	247 (22.8)	0.8
20:01–24:00	23 (16.0)	66 (15.6)	54 (19.2)	55 (16.4)	7 (15.9)	0.79	182 (16.8)	0.86
SBP, median (IQ), mm Hg								
Prehospital	151 (136–178)	154 (138–174)	150 (136–176)	158 (140–174)	152.5 (141–177)	0.44	155 (138–175)	0.51
DBP, median (IQ), mm Hg								
Prehospital	89 (22)	89 (76–100)	84 (74–96)	89.5 (76–100)	82 (77–95)	0.058	88 (76–100)	0.85
Presenting stroke features								
LAMS-prehospital, median (IQ)	4 (3–5)	4 (3–5)	4 (3–5)	3 (2–5)	4 (2.3–5)	<0.001*	4 (3–5)	0.007*
LAMS-prehospital, mean (SD)	4.0 (1.2)	3.8 (2)	3.6 (1.3)	3.4 (1.4)	3.6 (2.3)	<0.001*	3.6 (1.3)	0.003*
GCS-prehospital, median (IQ)	15 (13–15)	15 (13–15)	15 (14,15)	15 (15)	15 (14.3–15)	0.043*	15 (14,15)	0.24
GCS-prehospital, mean (SD)	13.9 (2.1)	13.8 (2.2)	14.1 (1.6)	14.2 (1.7)	14.2 (1.6)	0.05*	14 (1.9)	0.37
NIHSS-early hospital, median (IQ)	6 (2–15)	9 (3–16)	7 (2–15)	6 (2–13)	8.8 (4–14.8)	0.003*	7 (3–15)	0.17
NIHSS-aphasia, n (%)	41 (28.5)	131 (30.9)	81 (28.8)	80 (23.8)	15 (34.1)	0.21	307 (28.3)	0.79
NIHSS-neglect, n (%)	43 (29.9)	150 (35.4)	85 (30.3)	72 (21.4)	14 (31.8)	0.002*	321 (29.6)	0.72
Side of weakness						0.80		0.67
Right	59 (41.0)	163 (38.4)	115 (40.9)	139 (41.4)	18 (40.9)		435 (40.1)	
Left	82 (56.9)	260 (61.3)	164 (58.4)	193 (57.4)	26 (59.1)		643 (59.3)	
Both‡	2 (1.4)	1 (0.2)	3 (1.1)	4 (1.2)	0 (0)		8 (0.7)	
Final diagnosis, n (%)						0.77		0.58
Ischemic stroke	123 (85.4)	356 (84.0)	234 (83.3)	276 (82.1)	39 (88.6)		905 (83.4)	
TIA	21 (14.58)	68 (16.0)	47 (16.7)	60 (17.9)	5 (11.4)		180 (16.6)	

DBP indicates diastolic blood pressure; GCS, Glasgow Coma Scale; LAMS, Los Angeles Motor Scale; LKWT, last known well time; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and TIA, transient ischemic attack.

*Statistically significant values based on $P<0.05$.

†Number and proportion of patients with last known well times at different times of 24-h day, in 4 h increments.

‡The uncommon patients with bilateral weakness are shown for descriptive purposes but were not included in the statistical calculation for laterality.

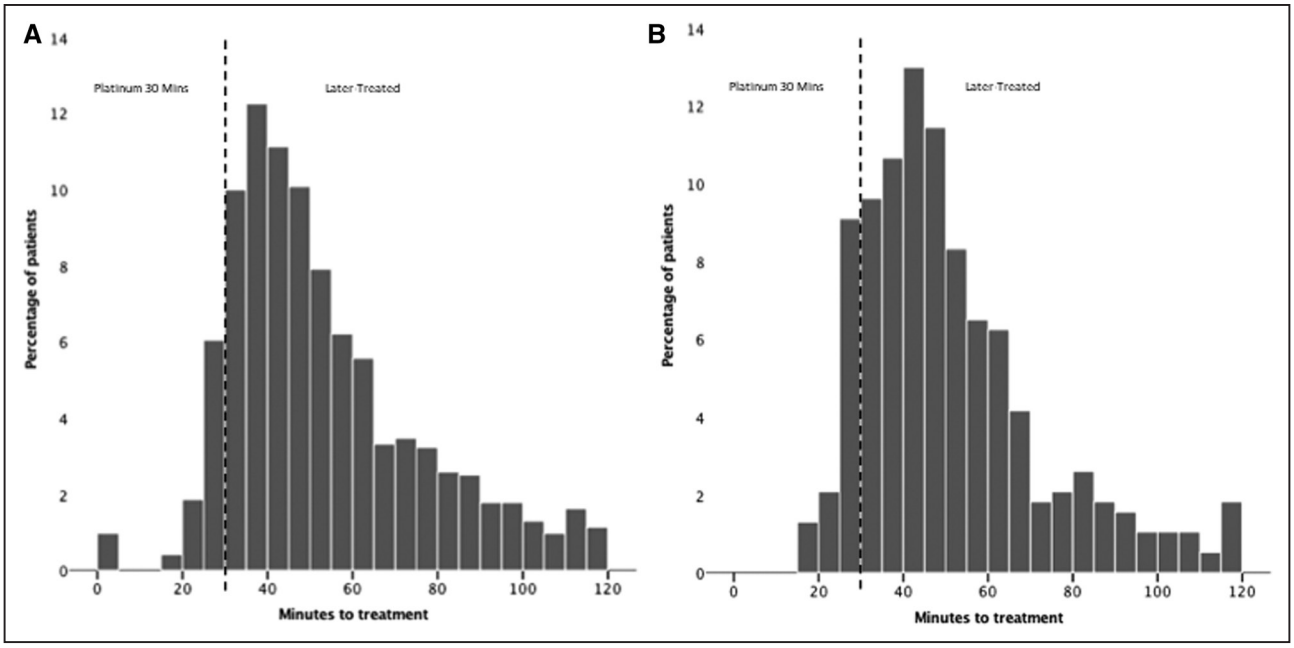

Figure 1. Histogram showing proportions of patients treated in 5 min intervals from 0–120 min.
A, Acute cerebral ischemia patients. **B**, Intracranial hemorrhage patients.

C statistic 0.66. A multivariate additive logistic regression model incorporating just the 7 baseline covariates identified as most predictive in the gradient boost analysis (LAMS, GCS, race, time of day of onset, systolic blood pressure, and diastolic blood pressure) performed similarly, C statistic 0.65. The classification tree modeling yielded 8 nodes incorporating 7 variables (LAMS, GCS, sex, history of hypertension, atrial fibrillation, alcohol, and diastolic blood pressure). The classification tree model also showed fair predictive performance, with C statistic of 0.63.

Among the 385 patients with ICH, median age was 64 (IQR, 55–76), 42.4% were women, and prehospital motor deficit severity on the LAMS was median 4 (IQR, 3–5). The median time from last known well to study agent start was 47 minutes (IQR, 37–62.5). The detailed distribution of onset-to-treatment times is shown in Figure 1B. The characteristics of patients in the binary categories of 1 to 30 minutes and >30 minutes and in the 5 more granular OTT categories are shown in Table 3. In the binary comparison of platinum half-hour patients versus later-treated patients, features distinguishing the groups were sex (more frequent in the platinum 30 minutes patients) and Hispanic ethnicity (less frequent in the platinum group).

The results of multivariate models to distinguish platinum half hour patients among ICH patients are shown in Table S2. The multivariate additive logistic regression model incorporating all 17 baseline covariates showed good predictive accuracy, with C statistic 0.72. In this model, sex, race, and ethnicity were statistically significant covariates. The classification tree model yielded 3 nodes incorporating 2 variables (GCS and sex). The classification tree model showed fair predictive performance, with C statistic of 0.63.

The global disability outcomes on the mRS at 90 days in the platinum half hour and later treated patients, for ACI patients and for ICH patients, are shown in Table 3 and Figure 2. The mRS outcomes for the all-patient population are shown in Table S3 and Figure S2. In all populations, global disability outcomes at 3 months were similar in platinum half hour and in later-treated patients in both bivariate and multivariate analysis. Among the ACI patients, the overall correlation between OTT and 90d mRS was r=–0.06; among the ICH patients, r=0.01.

DISCUSSION

This study finds that, with a strategy of prehospital initiation in a large multicenter trial, platinum half hour start of a potential neuroprotective agent was able to be achieved in a substantial proportion of acute ischemic and hemorrhagic stroke patients, accounting for more than 1 in 10 patients of all enrolled patients. Among patients with ACI, the strongest determinants of platinum half hour treatment status were more severe motor deficits on first prehospital assessment and younger age. Among ICH patients, the strongest associations with platinum half hour status were female sex, not being of Hispanic ethnicity, and more severe motor deficits prehospital. Global disability outcomes at 3 months on the mRS were similar among patients with OTT times within versus beyond the platinum half hour.

These patient features associated with platinum half hour status are biologically and clinically plausible. The association of more severe motor deficits with platinum half hour treatment in both acute cerebral ischemic and hemorrhagic stroke patients indicates that speed of call

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Table 2. Descriptive Characteristics of Platinum Half-Hour and Later-Treated Intracranial Hemorrhage Patients

	15–30 m (N=53)	31–45 m (N=132)	46–60 m (N=96)	61–120 m (N=96)	>120 m (N=8)	*P* value (comparing 5 groups)	>30 m (N=332)	*P* value (comparing 15–30 m and >30 m)
Age, median (IQ) y	66 (55.5–74.5)	63.5 (55–77)	64 (52.3–75)	66.5 (55–77.8)	60.5 (52.3–77.3)	0.69	64 (54–76)	0.64
Sex, n (%)								
Female	28 (52.8)	37 (28)	37 (38.5)	26 (27.1)	0 (0)	0.001*	100 (30.1)	0.001*
Race, n (%)						0.44		0.84
White	44 (83.0)	105 (79.6)	77 (79.4)	71 (74)	8 (100)		261 (78.6)	
Black	3 (5.7)	14 (10.6)	5 (5.2)	14 (14.6)	0		33 (9.9)	
Asian	5 (9.4)	12 (8.4)	13 (13.4)	8 (8.3)	0		33 (9.9)	
Other	1 (1.9)	1 (0.8)	1 (1)	3 (3.1)	0		5 (1.5)	
Hispanic ethnicity, n (%)	11 (20.8)	41 (31.1)	36 (37.5)	35 (36.5)	6 (75)	0.02*	118 (35.5)	0.03*
Medical Hx, n (%)								
Hypertension	40 (75.5)	103 (78)	75 (78.1)	81 (84.4)	4 (50)	0.19	263 (79.2)	0.54
Diabetes	8 (15.1)	21 (15.9)	21 (21.9)	19 (19.8)	3 (37.5)	0.45	64 (19.3)	0.47
Hyperlipidemia	18 (34.0)	58 (43.9)	35 (36.5)	28 (29.2)	1 (13.5)	0.11	122 (36.8)	0.70
Atrial fibrillation	4 (7.6)	10 (7.6)	7 (7.3)	9 (9.4)	0	0.98	26 (7.8)	0.60
Prior stroke/TIA	3 (5.7)	17 (12.9)	10 (10.4)	12 (12.5)	0	0.68	39 (11.8)	0.33
Tobacco use	9 (17)	20 (15.2)	18 (18.8)	17 (17.7)	1 (12.5)	0.96	56 (16.9)	0.98
Any alcohol use	23 (43.4)	53 (40.2)	51 (53.1)	43 (44.8)	2 (25)	0.27	149 (44.9)	0.85
LKWT, n (%)†						0.44		0.55
0001–0400	1 (1.9)	2 (1.5)	3 (3.1)	4 (4.2)	0 (0)	0.73	9 (2.7)	0.59
0401–0800	3 (5.7)	10 (7.6)	15 (15.6)	11 (11.5)	2 (25)	0.12	38 (11.5)	0.15
0801–1200	12 (22.6)	34 (25.8)	24 (25)	31 (32.3)	1 (12.5)	0.60	90 (27.1)	0.61
1201–1600	11 (20.8)	27 (20.5)	16 (16.7)	19 (19.8)	1 (12.5)	0.94	63 (19)	0.85
1601–20:00	19 (35.9)	40 (30.3)	19 (19.8)	21 (21.9)	3 (37.5)	0.11	83 (25)	0.13
20:01–24:00	7 (13.2)	18 (13.6)	19 (19.8)	9 (9.4)	1 (12.5)	0.35	47 (14.2)	0.52
SBP, median (IQ), mm Hg								
Prehospital	174 (154–196)	178 (160–194)	177 (160–195)	172.5 (160–192)	156.5 (142–205)	0.73	176 (160–194)	0.18
DBP, median (IQ), mm Hg								
Prehospital	100 (89–111)	100 (86–114)	100 (82–110)	100 (88–110)	98 (85–126)	0.24	100 (86–110)	0.38
Presenting stroke features								
LAMS-prehospital, median (IQ)	4 (4,5)	5 (3–5)	4 (3–5)	4 (3–5)	3 (2–3.8)	0.007	4 (3–5)	0.16
LAMS-prehospital, mean (SD)	4.41.2	4.15 (1.2)	4.1 (1.1)	3.9 (1.1)	2.75 (1)	0.004	4.1 (1.2)	0.08*
GCS-prehospital, median (IQ)	15 (15)	15 (14,15)	15 (15)	15 (15)	15 (15)	0.19	15 (15)	0.36
GCS-prehospital, mean (SD)	14.6 (1.2)	14.2 (1.6)	14.3 (1.6)	14.5 (1.3)	14.9 (0.4)	0.20	14.3 (1.5)	0.28
NIHSS-early hospital, median (IQ)	15 (9.5–24)	18.5 (11–29)	15 (9–26.8)	16.5 (7–25)	13 (11.3–21.8)	0.66	16 (9–2)	0.93
NIHSS-aphasia, n (%)	18 (34)	62 (47)	37 (38.5)	35 (36.8)	5 (62.5)	0.23	139 (41.9)	0.28
NIHSS-neglect, n (%)	29 (54.7)	67 (51.2)	50 (52.1)	43 (45.3)	3 (37.5)	0.70	163 (49.1)	0.45
Side of weakness						0.67		0.31
Right	17 (32.1)	60 (45.5)	34 (35.4)	38 (39.6)	4 (50)		136 (41)	
Left	35 (66)	71 (53.8)	61 (63.5)	58 (60.4)	4 (50)		194 (58.4)	
Both‡	1 (1.9)	1 (0.8)	1 (1)	0 (0)	0 (0)		2 (0.6)	
Final diagnosis, n (%)						0.34		0.32
Intracerebral hemorrhage	53 (100)	128 (97)	94 (97.9)	96 (100)	8 (100)		326 (98.2)	
Intracranial hemorrhage	0 (0)	4 (3)	2 (2.08)	0 (0)	0 (0)		6 (1.8)	

DBP indicates diastolic blood pressure; GCS, Glasgow Coma Scale; LAMS, Los Angeles Motor Scale; LKWT, last known well time; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and TIA, transient ischemic attack.

*Statistically significant values based on $P<0.05$.

†Number and proportion of patients with last known well times at different times of 24-h day, in 4 h increments.

‡The uncommon patients with bilateral weakness are shown for descriptive purposes but were not included in the statistical calculation for laterality.

Table 3. Ninety-Day Outcomes in Platinum Half-Hour and Later-Treated Groups

Acute cerebral ischemia									
Final 3 m outcome	15–30 m (N=144)	31–45 m (N=424)	46–60 m (N=281)	61–120 m (N=336)	>120 m (N=44)	*P* value (comparing 5 groups)	>30 m (N=1085)	Unadjusted *P* value comparing 15–30 vs 31–120	Adjusted *P* value comparing 15–30 vs 31–120†
mRS score 0–1 (non-disabled), n (%)	61 (42.4)	197 (46.5)	119 (42.3)	155 (46.1)	10 (22.7)	0.03*	481 (44.3)	0.73	0.92
mRS score 0–2 (independent), n (%)	89 (61.8)	248 (58.5)	158 (56.2)	199 (59.2)	20 (45.5)	0.27	625 (57.6)	0.26	0.17
mRS, median (IQ)	2 (0–4)	2 (0–4)	2 (0–4)	2 (1–4)	3 (2–4.8)	0.10	2 (0–4)	0.31	…
mRS, mean (SD)	2.19 (2.1)	2.33 (2.1)	2.39 (2.1)	2.28 (2)	3.05 (1.9)	0.18	2.36 (2.1)	0.37	…
Mortality, n (%)	19 (13.2)	53 (12.5)	37 (13.2)	37 (11)	8 (18.2)	0.72	135 (12.4)	0.76	0.76
Intracranial hemorrhage									
Final 3 m outcome	15–30 m (N=53)	31–45 m (N=132)	46–60 m (N=96)	61–120 m (N=96)	>120 m (N=8)	*P* value (comparing 5 groups)	>30 m (N=332)	Unadjusted *P* value comparing 15–30 vs 31–120	Adjusted *P* value comparing 15–30 vs 31–120‡
mRS score 0–1 (non-disabled), n (%)	8 (15.1)	11 (8.3)	9 (9.4)	7 (7.3)	0 (0)	0.48	27 (8.1)	0.11	0.09
mRS score 0–2 (independent), n (%)	15 (28.3)	38 (28.8)	33 (34.4)	24 (25)	4 (50)	0.45	99 (29.8)	0.78	0.53
mRS, median (IQ)	5 (2–6)	4 (2–6)	4 (2–5)	4 (2–6)	3 (2–5)	0.57	4 (2–6)	0.53	…
mRS, mean (SD)	4 (1.9)	3.9 (1.8)	3.7 (1.8)	4 (1.7)	3.4 (1.5)	0.68	3.9 (1.8)	0.53	…
Mortality, n (%)	16 (30.2)	36 (27.3)	23 (24)	28 (29.2)	0 (0)	0.37	87 (26.2)	0.58	0.89

ACI indicates acute cerebral ischemia; LAMS, Los Angeles Motor Scale; and mRS, modified Rankin Scale.
*Statistically significant values based on $P<0.05$.
†For ACI, adjustment variables were age, hypertension, prehospital LAMS, tobacco.
‡For ICH, adjustment variables were: sex, Hispanic ethnicity, systolic blood pressure, prehospital LAMS.

to the EMS system by patients or on-scene witnesses is driven in part by deficit severity. The stronger association of deficit severity with platinum half hour presentation for ACI patients than ICH patients likely reflects that early EMS contact in hemorrhage patients is also driven by discomforting symptoms of headache and nausea. Among ACI patients, the association of younger age with platinum half hour treatment may reflect greater social engagement (more opportunity for witnesses to observe onset) and less baseline cognitive disturbance and preexisting disability interfering with patient symptom recognition. Among intracerebral hemorrhage patients, the association of female sex with increased platinum half hour treatment is speculative but may reflect earlier onset of headache in ICH patients with a background disposition to migraine, with headache prompting earlier EMS contact. The association of Hispanic ethnicity with reduced platinum half-hour treatment may reflect lack of awareness of cerebrovascular disease and the need to activate the EMS system, hesitancy to incur healthcare costs by activating EMS, and language communication barriers.[22,23]

However, the variables associated with platinum half hour status among ACI patients had only modest determinative value, with multivariable model predictive performance only in the fair range. These results indicate that platinum half hour ACI patients are broadly similar in demographic and clinical variables to later presenting patients, even though they almost certainly differ in having more favorable penumbral profiles.[24,25] This finding suggests that treatments found beneficial in platinum half hour patients are likely also to be of benefit for later-presenting patients harboring salvageable tissue, rather than being limited by distinctive demographic and clinical patient features. In contrast, the variables associated with platinum half hour status among ICH patients showed good multivariate determinative value. As Hispanic ethnicity was an important factor in late presentation, this finding highlights the need to address ongoing disparities in early access to the medical system.

It is noteworthy that 3 month outcomes did not differ among platinum half-hour patients and later-treated patients. This result indicates that platinum half-hour presentation, compared with slightly later presentation, has only limited prognostic value regarding final outcome. However, once a beneficial therapy able to be started in ambulances becomes available, platinum half hour treatment is likely to be associated with maximal intervention benefit. Platinum half hour status would then be a biomarker that is predictive but not prognostic.[26]

This study has limitations. Our analysis included only those patients who were enrolled in a clinical trial. Though the trial entry criteria were broad in age, stroke severity,

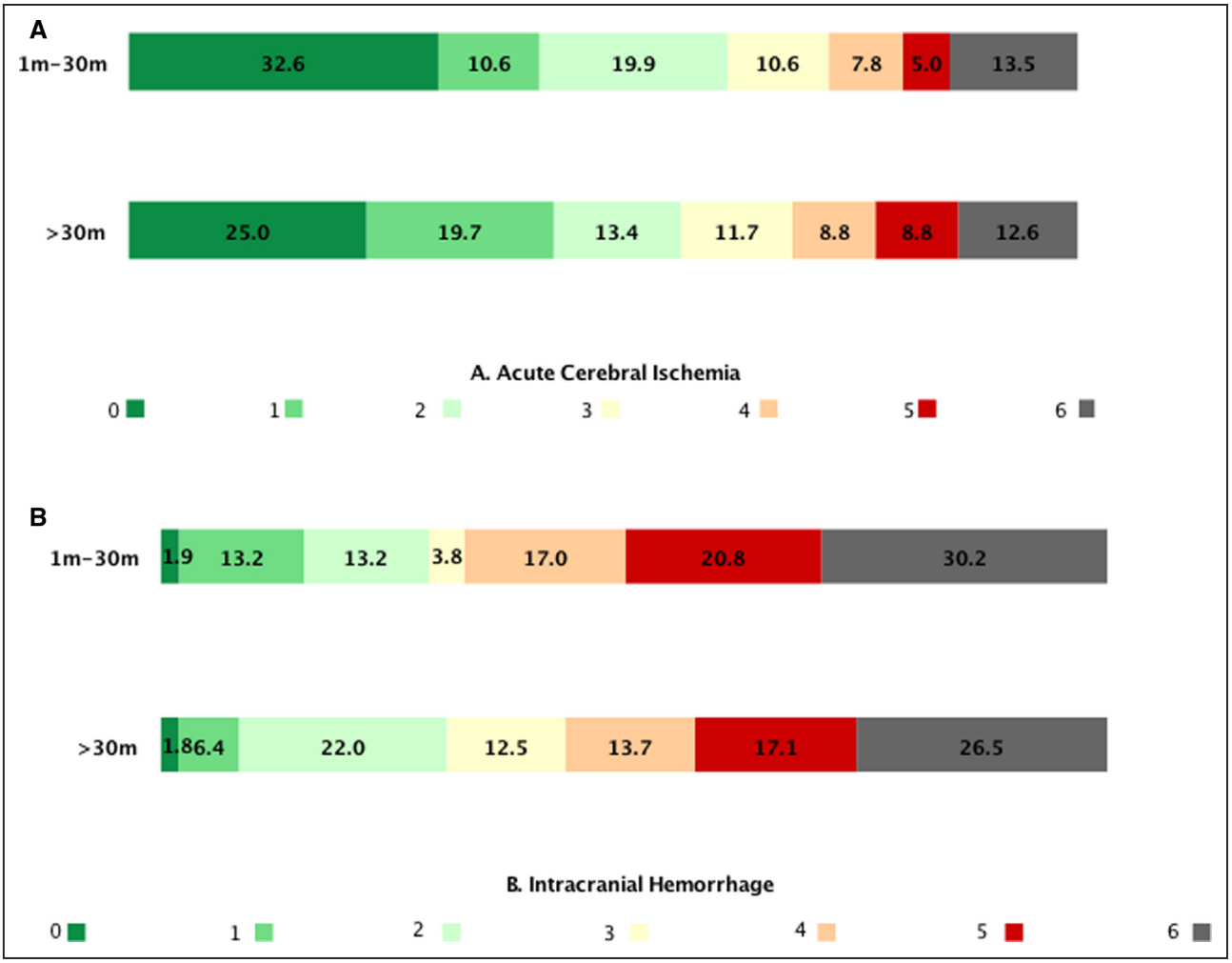

Figure 2. Global disability modified Rankin Scale outcome distributions at 90 d in platinum half-hour and later-treated patients. **A**, Acute cerebral ischemia patients. **B**, Intracranial hemorrhage patients.

and comorbidities,[17] the study did exclude patients with uncommon features such as prestroke disability and systolic blood pressure higher than 220 mm Hg. Such patients may have different frequencies of platinum-half hour presentation. Early vessel imaging after hospital arrival was not obtained routinely in studied patients, so the effect of presence or absence of large vessel occlusion upon platinum-half hour presentation in acute cerebral ischemic could not be explored. While initial brain imaging was obtained in all patients, follow-up imaging was not mandated and varied in timing and components with local practice. As a result, the study did not address the frequencies of postarrival infarct growth or hematoma expansion in platinum half-hour compared with later-treated patients.

CONCLUSIONS

Paramedic prehospital initiation of neuroprotection study agent permits treatment start within the platinum first 30 minutes in a substantial proportion of acute ischemic and hemorrhagic stroke patients, accounting for more than 1 in 10 patients enrolled in a multicenter trial. Hyperacute platinum half hour patients were largely similar to later-treated patients and are an attainable target for treatment in prehospital stroke trials.

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Affiliations

California University of Science and Medicine, School of Medicine, Colton (A.S.R.). National University of Cajamarca, School of Medicine, Cajamarca, Peru (F.P.-V.). Departments of Emergency Medicine and Neurology (S.S., S.S.), Department of Neurology (D.S.L., G.A., L.S., L.R.-J., M.V.-S., J.L.S.), and Department of Neuroradiology (P.V.), University of California Los Angeles David Geffen School of Medicine. Department of Neurology University of Southern California, Los Angeles (N.S., M.K.-T.). Department of Computational Medicine, University of California, Los Angeles (J.G.). National Institute of Neurological Disorders and Stroke, National Institutes of Health, Neuroscience Center, Bethesda, MD (R.C.). Department of Neurology, Stanford University, Palo Alto, CA (S.H.).

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Supplemental Material

Checklist
Supplemental Results
Tables S1–S3
Figures S1–S2

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