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Hospital distance, socioeconomic status, and timely treatment of ischemic stroke

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Abstract

Objective

To determine whether lower socioeconomic status (SES) and longer home to hospital driving time are associated with reductions in tissue plasminogen activator (tPA) administration and timeliness of the treatment.

Methods

We conducted a retrospective observational study using data from the Get With The Guidelines–Stroke Registry (GWTG-Stroke) between January 2015 and March 2017. The study included 118,683 ischemic stroke patients age ≥18 who were transported by emergency medical services to one of 1,489 US hospitals. We defined each patient's SES based on zip code median household income. We calculated the driving time between each patient's home zip code and the hospital where he or she was treated using the Google Maps Directions Application Programing Interface. The primary outcomes were tPA administration and onset-to-arrival time (OTA). Outcomes were analyzed using hierarchical multivariable logistic regression models.

Results

SES was not associated with OTA (p = 0.31) or tPA administration (p = 0.47), but was associated with the secondary outcomes of onset-to-treatment time (OTT) (p = 0.0160) and in-hospital mortality (p = 0.0037), with higher SES associated with shorter OTT and lower in-hospital mortality. Driving time was associated with tPA administration (p < 0.001) and OTA (p < 0.0001), with lower odds of tPA (0.83, 0.79–0.88) and longer OTA (1.30, 1.24–1.35) in patients with the longest vs shortest driving time quartiles. Lower SES quintiles were associated with slightly longer driving time quartiles (p = 0.0029), but there was no interaction between the SES and driving time for either OTA (p = 0.1145) or tPA (p = 0.6103).

Conclusions

Longer driving times were associated with lower odds of tPA administration and longer OTA; however, SES did not modify these associations.

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Glossary

API = Application Programming Interface; **CI** = confidence interval; **DCRI** = Duke Clinical Research Institute; **EMS** = emergency medical services; **GEE** = generalized estimating equation; **GWTG-Stroke** = Get With The Guidelines–Stroke; **IA** = intra-arterial; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **OTA** = onset to arrival time; **OTT** = onset to treatment time; **SES** = socioeconomic status; **sICH** = symptomatic intracranial hemorrhage; **tPA** = tissue plasminogen activator.

Only 7% of patients hospitalized with acute ischemic stroke receive IV tissue plasminogen activator (tPA).[1] While recent studies[2,3] demonstrate the efficacy associated with expanded time windows for reperfusion, earlier thrombolysis leads to better outcomes.[4]

Socioeconomic status (SES), measured by zip code median income, has been shown to be associated with less timely tPA access.[5] Timely stroke treatment may also be impeded by the distance that patients need to travel in order to get to a tPA-capable facility.[6–11]

We were interested in further investigating the effects of low SES on timely ischemic stroke treatment, and to determine whether longer driving times may account for low SES patients having longer onset to arrival times (OTA) and lower odds of tPA administration. Low SES patients may have longer driving times than high SES patients, and low SES, through delayed emergency medical services (EMS) activation or responsiveness, may amplify the association with driving time.[12]

Using data from the American Heart Association's Get With The Guidelines–Stroke program (GWTG-Stroke), we sought to determine whether patients with low SES and patients with longer driving times transported by EMS have longer OTA or a lower frequency of tPA administration. We also wanted to know whether patients of low SES have longer driving times than patients of high SES, and whether SES modifies the association between driving time and OTA or tPA administration. This analysis assesses whether there are certain populations who are particularly vulnerable to delayed arrival, such as low SES patients who live far from the hospital.

Methods

Data collection

Data were collected from the American Heart Association GWTG-Stroke, a voluntary national registry database, which, since 2003, has collected a range of data from hospitals across the United States about patients with a diagnosis of stroke. Collected data include information such as stroke etiology, patient demographics, medical history, symptom and treatment timeline, and patient outcomes. The range of GWTG-Stroke variables, the collection methodology, and the validity and reliability of the measures has been described previously.[13–15]

Population

The study population includes adult patients (age ≥18) who had a final diagnosis of ischemic stroke from January 2015 (when GWTG-Stroke zip code information first became available) to March 2017. Patients were limited to those who were treated at a site that recorded >25% of requested patient medical history to GWTG-Stroke. The study includes patients who had an onset of symptoms in a non–health care setting and were brought to the hospital by EMS. We limited the analysis to patients brought in by EMS in order to focus on the role of SES and distance among EMS care. To be included, patients were required to have a recorded home zip code that was geocodable, within one of the 48 contiguous United States, and less than 100 miles from the treatment hospital. Patients were excluded if they were transferred from another hospital for IV tPA or intra-arterial (IA) catheter-based treatment, or if they received these treatments from the transferring hospital. Patients were also excluded if they had an OTA greater than 24 hours, as these patients were unlikely to receive timely reperfusion regardless of driving time. For the analysis of driving time and tPA administration only, patients were excluded if they had documented contraindications or warnings to receiving tPA (figure).

Study measures

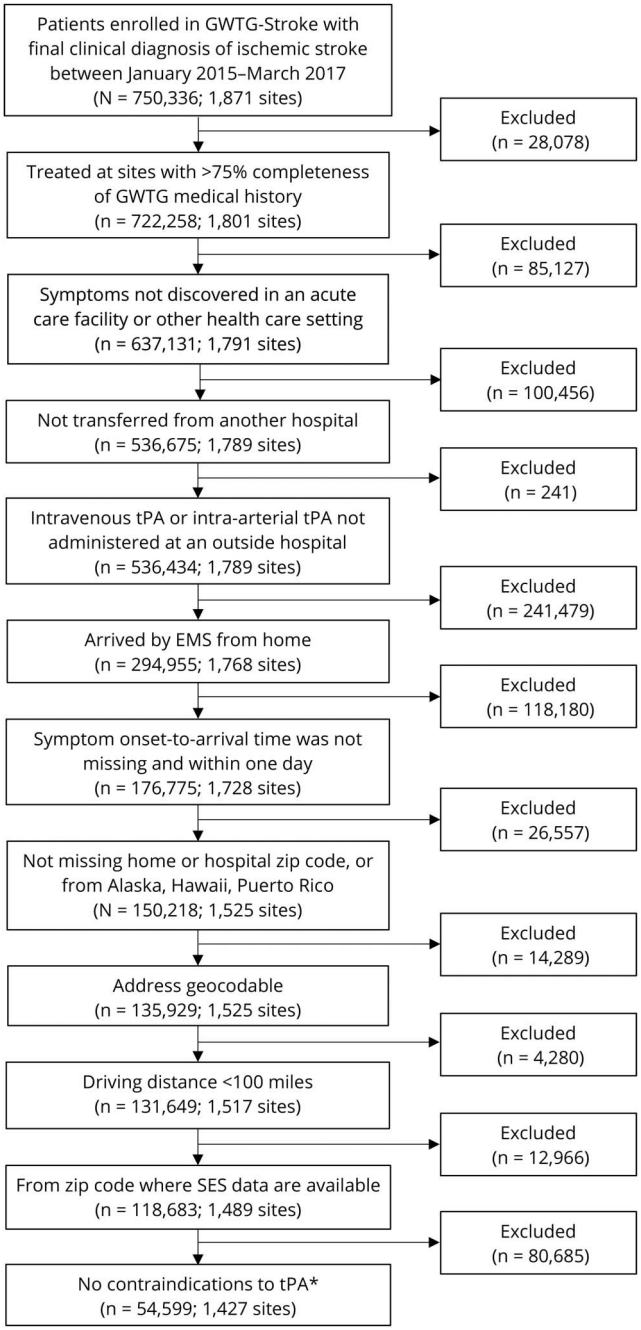
We determined the SES of each patient's home zip code by determining his or her zip code median household income, based on 2015 US Census data.[16] Patients were then classified according to zip code median household income quintile, based on the total study population.

Driving times were estimated based on the patient's home zip code and the address of the treating hospital. We first used the SAS geocode procedure to identify the geographic coordinates of each patient's home zip code.[17] We used the same procedure to determine the geographic coordinates of the treatment hospital street address. We then applied the patient home and hospital geographic coordinates, along with the hospital arrival time, to the Google Maps Directions Application Programming Interface (API). The Directions API uses Google Maps traffic data to calculate the driving time between the patient home zip code geographic coordinates and the hospital geographic coordinates.[18] After determining individual driving times, patients were classified according to driving time quartiles.

Outcomes

The primary outcomes are OTA and tPA administration. To determine OTA, we calculated the difference between the date/time of discovery of stroke symptoms and the date/time

Figure Inclusion/exclusion criteria



*Exclusion of patients with contraindications to tissue plasminogen activator (tPA) was applied only to the tPA analysis. EMS = emergency medical services; GWTG-Stroke = Get With The Guidelines–Stroke; SES = socioeconomic status.

of arrival to the hospital. We then classified patients according to the following OTA categories: <2 hours, 2–3.5 hours, 3.5–6 hours, >6 hours.

Patients who received IV tPA or IA tPA were identified based on documentation of these procedures in GWTG-Stroke.

As secondary outcomes, we determined each patient's onset to treatment time (OTT) (<2 hours, 2–3.5 hours, 3.5–6 hours, >6 hours), in-hospital mortality rate, discharge ambulatory status, discharge modified Rankin Scale (mRS) score (>2, >3 vs below), whether they were discharged to home, and whether they had a tPA complication of symptomatic intracranial hemorrhage (sICH) within 36 hours of tPA administration.

Statistical analysis

To assess home to hospital driving time, patient SES, and their interaction and association with the primary and secondary outcomes, we developed multivariable regression models using generalized estimating equation (GEE) to account for in-hospital clustering of patients. An ordinal logistic regression was run for the ordinal outcomes OTA and OTT and a binomial logistic regression was used for all other outcomes, which were binary. Hospital characteristics and patient variables were included in the GEE models. We used common variables for stroke standard analyses. The lists of variables were selected by clinicians and statisticians based on experience and previous model fitting. Hospital characteristics included in the models were bed size, acute ischemic stroke volume, tPA volume, region (Midwest, West, South, Northeast), urban/rural location, presence of a stroke center, and academic classification. Patient variables were age, sex, race, history of atrial fibrillation or flutter, previous stroke/TIA, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes (insulin and non-insulin-treated), peripheral vascular disease, hypertension, dyslipidemia, smoking, heart failure, and renal insufficiency. All of the variables were included in the model, regardless of statistical significance.

To determine whether SES modifies the association between driving time and the outcomes of interest (OTA and tPA), an SES quintile × driving time quartile interaction term was tested within each main effects model. Home zip code is used as a proxy for location of stroke onset; however, patients may have been away from home at the time of their stroke. To account for this, we included the variables "on hours" (weekdays 7 AM–5 PM) and "off hours" (weekdays 5 PM–7 AM, and all hours on Saturday and Sunday) in the GEE model, and assessed the interaction between off hour and driving time. Whenever an interaction term was deemed not significant ($p > 0.05$), we excluded it from the model.

Greater stroke severity, measured by NIH Stroke Scale (NIHSS), is likely associated with worse outcomes and different symptom onset to treatment times. Nevertheless, not all patients had their NIHSS measured. To account for this, we performed a sensitivity analysis, adjusting for NIHSS among patients with a completed NIHSS.

All variables had a low rate of missing data (<3%), except for NIHSS (4.9%), independent ambulation (7.1%), mRS at discharge (42.2%), and GWTG ischemic stroke–only estimated mortality rate (18.2%).

To assess the potential contribution of unmeasured confounding, E-values were calculated using the EValue package in R v3.2.5.[19] Variance explained by the logistic models was

Table 1 Demographics, baseline characteristics, and outcomes

	Overall (n = 118,683)	Quintile 1, <$46,400 (n = 23,727)	Quintile 2, $46,400–$52,136 (n = 23,833)	Quintile 3, $52,136–$57,895 (n = 23,673)	Quintile 4, $57,895–$70,150 (n = 23,740)	Quintile 5, >$70,150 (n = 23,710)	*p* Value[a]
Demographics							
Age (range 18–110), y[b]	74 (63–84)	72 (61–83)	73 (62–84)	74 (62–84)	75 (63–84)	76 (65–86)	<0.0001
Age ≥65 years	71.5	68.3	70.7	70.2	72.8	75.5	<0.0001
Female	51.5	51.6	51.1	51.3	51.3	52.0	0.3069
Ethnicity/race							
Hispanic	6.6	7.3	5.8	8.1	6.3	5.6	<0.0001
Non-Hispanic black	17.4	22.9	17.4	19.3	14.5	12.8	
Non-Hispanic white	69.7	66.2	72.5	67.3	71.0	71.3	
Other	6.4	3.7	4.3	5.3	8.2	10.3	
Estimated driving time, min	20.7 (13.5–32.2)	22.1 (14.5–33.2)	20.3 (13.2–31.2)	21.2 (13.5–33.5)	20.0 (13.0–30.7)	19.8 (13.1–31.2)	
Arrival and admission information							
Off-hours (5 PM–7 AM weekdays, all hours Saturday and Sunday) vs on-hours (7 AM–5 PM weekdays)	57.5	57.5	57.3	57.4	58.0	57.2	0.5522
Weekend arrival day	27.6	27.6	27.3	27.7	27.8	27.7	0.7562
Admission information							
First NIH Stroke Scale total score recorded by hospital personnel[b]	6 (2–13)	6 (3–14)	6 (2–13)	6 (2–12)	6 (2–13)	5 (2–12)	<0.0001
Onset to arrival time,[b] min	155 (64–484)	162 (70–487)	149 (63–467)	155 (64–493)	152 (61–475)	156 (63–495)	<0.0001
Onset to treatment time,[b] min	128 (97–170)	134 (102–174)	126 (96–170)	128 (97–170)	124 (94–167)	127 (96–168)	<0.0001
Discharge status							
Independent ambulation	41.7	40.5	40.9	41.5	42.4	43.0	<0.0001
Discharge to home	40.4	40.6	40.4	41.3	40.5	39.2	0.0001
Mortality							
In-hospital death (transfer-out patients excluded)	5.6	5.9	5.7	5.1	5.9	5.7	0.0019

Continued

Table 1 Demographics, baseline characteristics, and outcomes *(continued)*

	Overall (n = 118,683)	Quintile 1, <$46,400 (n = 23,727)	Quintile 2, $46,400–$52,136 (n = 23,833)	Quintile 3, $52,136–$57,895 (n = 23,673)	Quintile 4, $57,895–$70,150 (n = 23,740)	Quintile 5, >$70,150 (n = 23,710)	*p* Value[a]
IV tPA administration among patients with no contraindications (n = 54,599)	52.3	50.7	54.4	50.1	53.5	52.7	<0.0001
tPA complication of sICH within 36 hours among patients who received tPA (n = 28,545)	3.9	3.8	3.7	4.0	3.9	4.3	0.6217

Abbreviations: sICH = symptomatic intracranial hemorrhage; tPA = tissue plasminogen activator.
All tests treat the column variable as nominal. Values are n (%) or median (25th–75th percentile).
[a] *p* Values do not correspond to the table exactly as it is presented here. More appropriately, *p* values were calculated by comparing only nonmissing row values. *p* Values are based on Pearson χ^2 tests for all categorical row variables.
[b] *p* Values are based on χ^2 rank–based group means score statistics for all continuous/ordinal row variables. This is equivalent to Kruskal-Wallis tests.

calculated with the squared Pearson correlation method, while variance explained by the linear models was calculated directly from the model output in SAS.[20]

Data availability statement

Data were collected by the American Heart Association (the steward of the data according to contracts between the American Heart Association and participating hospitals), and are stored securely at the Duke Clinical Research Institute (DCRI). Given that data were collected for clinical care and quality improvement, rather than primarily for research, data sharing agreements require an application process in order for other researchers to access the data. Interested researchers can submit proposals to utilize GWTG for research purposes, including for validation purposes. Proposals can be submitted at heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-stroke/get-with-the-guidelines-stroke-overview. Additional information regarding the statistical analysis plan and analytic code may also be available from DCRI upon request.

Standard protocol approvals, registrations, and patient consents

All participating hospitals were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted waiver of informed consent under the common rule. The DCRI (Durham, NC) was granted institutional review board approval to analyze GWTG data for research.

Results

There were 118,683 patients from 1,489 hospitals included in the study (table 1). Patients had a median age of 74, were 51.5% female, 6.6% Hispanic, 17.4% non-Hispanic black, and 69.7% non-Hispanic white. Zip code median household income quintile boundaries at the 20th, 40th, 60th, and 80th percentiles were $46,400, $52,136, $57,895, and $70,150. Driving quartile boundaries were 13.5 minutes at the 25th percentile, 20.7 minutes at the 50th percentile, and 32.1 minutes at the 75th percentile. Patients had a median (interquartile range [IQR]) NIHSS of 6 (2–13) on arrival and a median OTA of 155 minutes (64–484). Among the 26.5% of patients who received IV tPA, there was a median OTT of 128 minutes (97–170). There was a 5.6% in-hospital mortality rate, and on discharge, 41.7% could independently ambulate and 40.4% were discharged to home.

The association between SES and the outcomes as well as driving time and the outcomes are shown in tables 2 and 3. There was no association between SES quintile and the primary outcomes of OTA ($p = 0.31$) or tPA administration ($p = 0.47$). However, there was an overall association between SES and OTT ($p = 0.02$) and SES and in-hospital mortality ($p = 0.004$).

Table 2 Association between socioeconomic status (SES) and outcomes in adjusted model[a]

Outcome	SES quintile ORs (reference quintile 1 <$46,400 OR [95% CI]), E-value of effect estimate (E-value of lower limit of 95% CI)				% Variance explained by models
	Quintile 2, $46,400–$52,136	Quintile 3, $52,136–$57,895	Quintile 4, $57,895–$70,150	Quintile 5, >$70,150	
Onset to arrival time	0.95 (0.90, 1.01) 1.19 (1.00)	0.98 (0.93, 1.04) 1.11 (1.00)	1.00 (0.94, 1.06) 1.00 (1.00)	1.01 (0.95, 1.07) 1.08 (1.00)	0.55
tPA administration	1.01 (0.93, 1.09) 1.08 (1.00)	0.98 (0.89, 1.07) 1.11 (1.00)	0.93 (0.86, 1.02) 1.23 (1.00)	0.96 (0.89, 1.05) 1.17 (1.00)	4.10
Onset to treatment time	0.87 (0.79, 0.96) 1.56 (1.25)	0.90 (0.81, 1.00) 1.46 (1.00)	0.83 (0.75, 0.93) 1.70 (1.36)	0.88 (0.79, 0.98) 1.53 (1.16)	0.23
In-hospital mortality	0.87 (0.78, 0.97) 1.56 (1.21)	0.79 (0.70, 0.88) 1.85 (1.53)	0.86 (0.77, 0.96) 1.60 (1.25)	0.84 (0.74, 0.94) 1.67 (1.32)	1.66
Modified Rankin Scale score >1 at discharge	0.95 (0.83, 1.08) 1.19 (1.00)	1.00 (0.87, 1.15) 1.00 (1.00)	0.98 (0.86, 1.12) 1.11 (1.00)	0.99 (0.86, 1.14) 1.07 (1.00)	7.11
Modified Rankin Scale score >2 at discharge	0.92 (0.82, 1.04) 1.25 (1.00)	1.04 (0.91, 1.18) 1.16 (1.00)	1.00 (0.87, 1.14) 1.00 (1.00)	0.96 (0.84, 1.11) 1.17 (1.00)	8.25
Independent ambulation at discharge	1.01 (0.91, 1.13) 1.08 (1.00)	0.99 (0.89, 1.11) 1.08 (1.00)	1.08 (0.96, 1.20) 1.24 (1.00)	1.08 (0.96, 1.20) 1.24 (1.00)	7.07
Discharge home	1.00 (0.94, 1.06) 1.00 (1.00)	1.05 (0.98, 1.12) 1.18 (1.00)	1.03 (0.97, 1.10) 1.14 (1.00)	1.02 (0.95, 1.08) 1.11 (1.00)	6.60
tPA complication of symptomatic intracranial hemorrhage within 36 hours of tPA administration	0.97 (0.79, 1.19) 1.21 (1.00)	1.05 (0.84, 1.31) 1.28 (1.00)	1.04 (0.85, 1.27) 1.24 (1.00)	1.11 (0.90, 1.36) 1.46 (1.00)	0.58

Abbreviations: CI = confidence interval; OR = odds ratio; tPA = tissue plasminogen activator.
[a] Model covariates: main variables of interest: driving time quartile, zip code household median income quintile. Patient-level characteristics: age, sex, insurance status, medical history of atrial fibrillation/flutter, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, hypertension, dyslipidemia, peripheral vascular disease, smoking status, prior heart failure, renal insufficiency, prior stroke/TIA, arrival time (off vs on hour). Hospital traits: annual volume of ischemic stroke admissions, annual volume of IV tPAs, number of beds in hospital, teaching hospital or not, rural location or not, region of hospital (Northeast, Midwest, South, West), primary stroke center or not.

As SES increased, OTT decreased and in-hospital mortality decreased (table 2). There was no association between SES quintile and mRS >1 ($p = 0.9408$), mRS >2 ($p = 0.4805$), ambulation at discharge ($p = 0.48$), discharge home ($p = 0.5191$), or tPA complication of sICH within 36 hours ($p = 0.83$).

There was an overall association between driving time and the primary outcomes of OTA ($p < 0.001$) and tPA administration ($p < 0.001$). In the shortest driving time (median minutes [IQR]) quartile (9.7 [7.1–11.8]), 58.2% of patients had an OTA under 3.5 hours, while in the longest driving time quartile (45.0 [37.6–59.3]), the percent decreased modestly to 52.7% (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.24–1.35). The percent of patients who received tPA decreased from 27.5% in quartile 1 to 23.9% in quartile 4 (OR 0.83, 95% CI 0.79–0.88) (table 4).

There was also an association between driving time and OTT ($p < 0.001$), and as driving time increased, OTT increased (quartile 4 OR 1.40, 95% CI 1.30–1.50, compared to quartile 1). There were also associations between driving time and discharge to home ($p < 0.0001$), ambulation at discharge ($p = 0.0003$), and mRS >2 ($p = 0.0086$); however, there was no clear pattern for these associations (table 3). The association of driving time with in-hospital mortality was borderline ($p = 0.0517$). There was no association between driving time and tPA complication of sICH within 36 hours.

There was no interaction between the SES × driving time interaction term and OTA ($p = 0.11$) or tPA administration ($p = 0.61$) and any of the primary or secondary outcomes. However, there was a small association between SES quintile and driving time quartile, such that lower SES was correlated with longer driving times ($r = -0.04$, $p = 0.0029$).

There was no interaction between off hours and driving time for OTA ($p = 0.34$), tPA administration ($p = 0.97$), or any of the secondary outcomes (table 5). Compared with patients with NIHSS recorded, those without NIHSS recorded were less likely to come from an academic hospital (54.3% vs 58%, $p = 0.0007$), were more likely to come from a rural hospital (7.5% vs 3.6%, $p < 0.0001$), and had longer OTA times (299 vs 149 minutes, $p < 0.0001$) (table e-1, doi.org/10.5061/dryad.60j13b7). The sensitivity analysis adjusting for NIHSS demonstrated similar results to the primary analysis, with significant associations between driving time and all outcomes other than in-hospital mortality, mRS, and tPA complications (table 6).

Table 3 Association between home and hospital driving time and outcomes in adjusted model[a]

Outcome	Driving time quartile ORs (reference quartile 1 [0–13.5 min] OR [95% CI]), E-value of effect estimate (E-value of lower limit of 95% CI)			% Variance explained by models
	Quartile 2, 13.5–20.7 min	Quartile 3, 20.7–32.1 min	Quartile 4, 32.2–180.4 min	
Onset to arrival time	1.02 (0.98, 1.06) 1.11 (1.00)	1.04 (1.00, 1.07) 1.16 (1.00)	1.30 (1.24, 1.35) 1.54 (1.47)	0.55
tPA administration	0.99 (0.95, 1.03) 1.08 (1.00)	1.00 (0.96, 1.05) 1.00 (1.00)	0.83 (0.79, 0.88) 1.43 (1.33)	4.10
Onset to treatment time	0.99 (0.93, 1.06) 1.11 (1.00)	1.03 (0.96, 1.10) 1.21 (1.00)	1.40 (1.30, 1.50) 2.15 (1.92)	0.23
In-hospital mortality	0.93 (0.87, 1.00) 1.36 (1.00)	1.03 (0.96, 1.11) 1.21 (1.00)	1.01 (0.94, 1.09) 1.11 (1.00)	1.66
Modified Rankin Scale score >1 at discharge	0.95 (0.89, 1.01) 1.19 (1.00)	0.96 (0.89, 1.04) 1.17 (1.00)	1.03 (0.95, 1.12) 1.14 (1.00)	7.11
Modified Rankin Scale score >2 at discharge	0.96 (0.90, 1.02) 1.17 (1.00)	0.92 (0.86, 0.99) 1.25 (1.08)	1.03 (0.95, 1.11) 1.14 (1.00)	8.25
Independent ambulation at discharge	1.02 (0.97, 1.07) 1.11 (1.00)	1.07 (1.01, 1.13) 1.22 (1.08)	0.95 (0.89, 1.01) 1.19 (1.00)	7.07
Discharge home	1.02 (0.98, 1.06) 1.11 (1.00)	1.02 (0.98, 1.06) 1.11 (1.00)	0.94 (0.90, 0.98) 1.21 (1.11)	6.60
tPA complication of symptomatic intracranial hemorrhage within 36 hours of tPA administration	1.03 (0.87, 1.21) 1.21 (1.00)	0.94 (0.79, 1.13) 1.32 (1.00)	0.98 (0.82, 1.17) 1.16 (1.00)	0.58

Abbreviations: CI = confidence interval; OR = odds ratio; tPA = tissue plasminogen activator.
[a] Model covariates: main variables of interest: driving time quartile, zip code household median income quintile. Patient-level characteristics: age, sex, insurance status, medical history of atrial fibrillation/flutter, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, hypertension, dyslipidemia, peripheral vascular disease, smoking status, prior heart failure, renal insufficiency, prior stroke/TIA, arrival time (off vs on hour). Hospital traits: annual volume of ischemic stroke admissions, annual volume of IV tPAs, number of beds in hospital, teaching hospital or not, rural location or not, region of hospital (Northeast, Midwest, South, West), primary stroke center or not.

Discussion

For this nationally representative cohort of patients hospitalized with acute ischemic stroke, we sought to determine whether patients with low SES and patients with longer driving times have longer OTA or lower tPA administration. Lower SES was not associated with longer OTA or lower rates of tPA administration, but was associated with longer OTT and higher in-hospital mortality. Longer driving times were associated with decreased odds of tPA administration, longer OTA, and longer OTT. Although low SES patients had slightly longer driving times than higher SES patients, SES did not modify the association between driving time and OTA or tPA administration.

Table 4 Percent of patients who received IV tissue plasminogen activator (tPA) or had onset to arrival time (OTA) <3.5 hours, by driving time quartile[a]

Outcomes	Driving time quartiles, median minutes (IQR), %			
	Quartile 1, 9.7 (7.1–11.8)	Quartile 2, 16.9 (15.2–18.7)	Quartile 3, 25.2 (22.8–28.3)	Quartile 4, 45.0 (37.6–59.3)
Received IV tPA	27.49	27.00	27.40	23.91
OTA <3.5 hours	58.15	57.72	57.60	52.74

Abbreviation: IQR = interquartile range.
[a] Analysis based on overall model, with identical covariates, including socioeconomic status.

Our findings support prior literature on the association of SES and timely treatment by demonstrating that low SES was significantly associated with greater OTT and in-hospital mortality.[5,21–23] Acute stroke treatment delays among low SES populations may be due to factors such as delayed EMS response, or lower levels of education leading to delayed recognition of stroke symptoms, lower awareness of treatment options, and subsequent delayed EMS activation.[21–23]

Studies of driving time and timely stroke treatment have had mixed results. While an analysis of data from a single hospital in St. Louis found greater patient distance from the hospital to be associated with a lower likelihood of tPA administration, they did not find distance to be associated with arrival time.[24] However, numerous other studies, including a national study in Japan by Kunisawa et al.,[25] did not find an association between patient distance and arrival time or tPA treatment.[25–28] Our study adds evidence that longer driving times are associated with reduced tPA administration, longer OTA, and worse patient outcomes.

Table 5 "On-hour" vs "off-hour" sensitivity analysis: Interaction between off hour × driving time quartile interaction term and outcomes

Outcome	χ^2	$P > \chi^2$
Onset to arrival time	3.39	0.3360
Onset to treatment time	0.59	0.8989
tPA administration	0.26	0.9668
In-hospital death	0.23	0.9733
Modified Rankin Scale score (>1)	1.00	0.8017
Modified Rankin Scale score (>2)	0.18	0.9802
Ambulate at discharge	2.33	0.5063
Discharge to home	4.90	0.1792
tPA complication within 36 hours	4.47	0.2154

Abbreviation: tPA = tissue plasminogen activator.

Patient arrival delays could be attributed to 2 processes: delays in EMS activation and delays in EMS transport. Our analysis, in light of existing literature, suggests that patients residing in a low SES zip code may have delays in EMS activation. In addition, driving time contributes to longer EMS transport times. Our data provide direction for further research addressing these 2 separate processes.

Our analysis demonstrates an association between SES and OTT, despite being limited to patients brought in by EMS. This suggests that delayed OTT among low SES patients can be attributed to either delayed ambulance activation or delayed transport time. We do not have information on when EMS was activated, and therefore cannot quantify the role of either delayed EMS activation or transport on delayed OTT. Prior research has demonstrated little difference in transport time in ischemic stroke for patients of different SES.[29] Thus, the delayed OTT among low SES patients can more likely be attributed to delayed EMS activation.

There have been a number of public education campaigns to increase recognition of stroke symptoms and rapid activation of EMS services. However, roughly one third of people in the United States are unaware of major stroke symptoms, with lower awareness and EMS use among black, Asian, and Hispanic populations.[30–32] Future research should determine how SES leads to delayed OTT and the types of education campaigns that would most effectively address this process.

The rate of tPA administration decreased modestly among the first 3 driving time quartiles, but decreased sharply among the fourth, longest driving time quartile. Similarly, the percentage of patients arriving within 3.5 hours decreased sharply in the quartile of patients with the longest driving times (table 4). Given these findings, policymakers should prioritize interventions that reduce transport time among this segment of the population that lives farthest from the hospital.

Table 6 NIH Stroke Scale (NIHSS) sensitivity analysis: NIHSS completed cases[a]

	NIHSS added as adjustment to interaction terms				NIHSS added as adjustment, interaction terms dropped			
	Driving time × SES quintile		Driving time × off hour		Driving time quartile		SES quintile	
Outcome	χ^2	$P > \chi^2$	χ^2	$P > \chi^2$	χ^2	$P > \chi^2$	χ^2	$P > \chi^2$
tPA administration	10.98	0.5304	0.01	0.9998	70.82	<0.0001	2.43	0.6568
Onset to arrival time	14.93	0.2456	1.34	0.7198	151.64	<0.0001	4.34	0.3620
Onset to treatment time	19.50	0.0771	0.61	0.8936	89.41	<0.0001	13.13	0.0106
In-hospital mortality	16.27	0.1791	0.39	0.9430	7.81	0.0501	7.72	0.1023
Modified Rankin Scale score (>1)	8.59	0.7372	1.99	0.5744	5.56	0.1349	1.96	0.7437
Modified Rankin Scale score (>2)	11.60	0.4780	0.43	0.9338	9.79	0.0205	4.99	0.2885
Ambulatory status (dichotomized at ambulate independently vs not)	9.35	0.6724	2.91	0.4059	17.32	0.0006	2.35	0.6721
Discharge home status (dichotomized as home vs not)	9.77	0.6361	4.09	0.2524	21.23	<0.0001	3.51	0.4757
tPA complication of symptomatic intracranial hemorrhage within 36 hours of tPA administration	19.20	0.0838	4.38	0.2230	1.05	0.7893	2.04	0.7284

Abbreviations: SES = socioeconomic status; tPA = tissue plasminogen activator.
[a] Model covariates: main variables of interest: driving time quartile, zip code household median income quintile. Patient-level characteristics: age, sex, insurance status, medical history of atrial fibrillation/flutter, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, hypertension, dyslipidemia, peripheral vascular disease, smoking status, prior heart failure, renal insufficiency, prior stroke/TIA, arrival time (off vs on hour). Hospital traits: annual volume of ischemic stroke admissions, annual volume of IV tPAs, number of beds in hospital, teaching hospital or not, rural location or not, region of hospital (Northeast, Midwest, South, West), primary stroke center or not. Model covariates as per table 3 with the addition of NIHSS.

There are a number of strategies that can be utilized to reduce transport time or to expand access to facilities that can offer tPA treatment. There are efforts to reduce the on-scene time of EMS and to expand the availability of acute stroke ready hospitals and primary and comprehensive stroke centers.[30,33] There is increasing use of telestroke services in lower population density regions and a strategy of transferring of patients from tPA-capable hospitals to hospitals with a higher level of care (drip and ship).[33] More recently, there has been use of ambulances with stroke diagnostic and treatment capabilities (mobile stroke units).[34] However, further research is needed to determine which policies most effectively improve timely stroke treatment for those patients who live farthest from the hospital.

Limitations

There are a number of limitations to our analysis. First, driving time was not measured directly, but rather was estimated using Google Maps. Second, the calculation of driving time was based on Google Maps traffic data available at the date and time of the analysis, not the date and time of the stroke. In addition, our calculations do not account for the fact that ambulances can bypass traffic and go faster than the speed limit. We did not have access to data on the speed of ambulances relative to non-EMS transit. In addition, we would not be able to apply any common adjustments to the calculated transit speeds, as the difference between EMS and non-EMS ground transportation likely differs between rural and urban settings, and regions with more or less traffic congestion. However, despite these limitations, the use of driving time is an improvement from using home to hospital linear distance, as the driving time calculation accounts for different traffic patterns of different regions. To account for the different transport speed of patients who were brought in by helicopter EMS, our analysis was limited to patients brought in by ground EMS. Third, we used patient home zip code as a proxy for the location of stroke onset. However, people are often away from home when their stroke occurs, and we did not have data for the location of stroke onset. To account for this, we performed a sensitivity analysis of strokes that occurred at times when patients were more and less likely to be at home, such as daytime vs nighttime and weekends, and found no significant differences. Fourth, we used the zip code median household income as a proxy for each patient's SES; however, this may not accurately represent each patient's SES. Fifth, excluding patients with tPA contraindications could have introduced a selection bias as tPA contraindications may be inadequately documented, especially in patients with longer driving times. Sixth, our study was limited to patients brought in by EMS. However, only about 50%–60% of stroke patients are brought in by EMS.[30,35] Seventh, given our lack of access to data from non-GWTG hospitals, we are unable to determine the representativeness of GWTG hospitals with regard to the driving times for patients living in low SES zip codes. However, the study included 1,489 GWTG hospitals across the 48 states, and we did not find a significant interaction between driving time and SES. Next, it is possible that OTT and OTA could be longer for patients living in zip codes where EMS programs were in place to route patients with possible large vessel occlusions to centers capable of mechanical thrombectomy. Even though our study data are recent (2015–2017), this limitation is largely theoretical, as many EMS agencies across the country likely did not have functional bypass polices in place. We do not have data regarding these zip code level EMS system protocols during the study period. In addition, GWTG-Stroke does not have data on when 911 was called, and we therefore cannot determine what proportion of OTA delay is due to delayed recognition of stroke symptoms or reluctance to call 911 vs delays in EMS response and transit. Finally, the associations between SES, driving time, and the outcomes could be explained by unmeasured confounders. However, the E-values demonstrate that these confounders would need to have moderately strong associations with SES, driving time, and the outcomes to explain the associations, and only a small portion of the variance of the outcomes was explained by the models.

Among patients with acute ischemic stroke, lower SES was associated with increased OTT and greater in-hospital mortality. Longer driving time was associated with decreased odds of tPA administration, longer OTA, and longer OTT. Although there was a small association between high SES and shorter driving times, SES did not modify the association between driving time and tPA administration or OTA. These findings provide evidence that SES and driving time to the hospital independently impede timely stroke treatment. Targeted interventions are needed to reduce EMS activation time for patients of low SES and transport time for patients who live far from tPA-capable hospitals.

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Jingjing Wu, MS	Duke Clinical Research Institute, Durham, NC	Author	Performed statistical analysis, revised the study design, interpreted the data, provided substantial revisions to the manuscript
Gregg C. Fonarow, MD	Division of Cardiology, Ronald Reagan–UCLA Medical Center, Los Angeles, CA	Author	Revised the study design, interpreted the data, provided substantial revisions to the manuscript
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Lee H. Schwamm, MD	Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Author	Revised the study design, interpreted the data, provided substantial revisions to the manuscript
Mathew J. Reeves, PhD	Department of Epidemiology, Michigan State University, East Lansing	Author	Revised the study design, interpreted the data, provided substantial revisions to the manuscript

Appendix *(continued)*

Name	Location	Role	Contribution
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