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Intravenous Tissue Plasminogen Activator in Stroke Mimics: Findings from the Get With The Guidelines Stroke Registry

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Abstract

Background—The necessity for rapid evaluation and treatment of acute ischemic stroke with intravenous tissue plasminogen activator (tPA) may increase the risk of administrating tPA to patients presenting with non-cerebrovascular conditions that closely resemble stroke ("stroke mimics"). However, there are limited data on thrombolysis safety in stroke mimics.

Methods and Results—Using data from the Get With The Guidelines Stroke Registry, we identified 72,582 suspected stroke patients treated with tPA from 485 US hospitals between January 2010 and December 2017. We documented the use of tPA in stroke mimics, defined as patients who present with stroke-like symptoms, but after work-up are determined not to have suffered from a stroke or transient ischemic attack, and compared characteristics and outcomes in stroke mimics versus those with ischemic stroke. Overall, 3.5% of tPA treatments were given to stroke mimics. Among them, 38.2% had a final non-stroke diagnoses of migraine, functional disorder, seizure, and electrolyte or metabolic imbalance. Compared with tPA-treated true ischemic strokes, tPA-treated mimics were younger (median 54 versus 71 years), had a less severe National Institute of Health Stroke Scale (median 6 versus 8), and a lower prevalence of cardiovascular risk factors, except for a higher prevalence of prior stroke/transient ischemic attack (31.3% vs. 26.1%, all p<0.001). The rate of symptomatic intracranial hemorrhage (sICH) was lower in stroke mimics (0.4%) as compared with 3.5% in ischemic strokes (adjusted OR 0.29, 95% CI 0.17–0.50). In-hospital mortality rate was significantly lower in stroke mimics (0.8% vs. 6.2%,

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adjusted OR 0.31, 95% CI 0.20–0.49). Patients with stroke mimics were more likely to be discharged to home (83.8% vs. 49.3%, adjusted OR 2.97, 95% CI 2.59–3.42) and to ambulate independently at discharge (78.6% vs. 50.6%, adjusted OR 1.86, 95% CI 1.61–2.14).

Conclusions—In this large cohort of patients treated with tPA, relatively few patients who received tPA for presumed stroke was ultimately not diagnosed with a stroke or TIA. The complication rates associated with tPA in stroke mimics were low. Despite the potential risk of administering tPA to stroke mimics, opportunity remains for continued improvement in the rapid and accurate diagnosis and treatment of ischemic stroke.

Intravenous recombinant tissue-type plasminogen activator (tPA) remains the mainstay of treatment of acute ischemic stroke.[1] The benefit of intravenous tPA, however is greatest when given early, and quickly declines with increasing time from stroke symptom onset to treatment initiation.[2, 3] Given the importance of reducing delay in treatment, the American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend intravenous tPA within 4.5 hours after stroke onset and the door-to-needle (DTN) time should be within 60 minutes from hospital arrival.[1] However, rapid delivery of thrombolytic therapy is challenging because ischemic stroke is commonly a clinical diagnosis – the most performed brain imaging modality (computed tomography) generally is used to rule out hemorrhage, rather than ruling in ischemic stroke. Therefore, the necessity for rapid thrombolysis may increase the likelihood of administrating tPA to patients with non-cerebrovascular conditions mimicking stroke, so-called “stroke mimics”.

Several studies have reported the prevalence and safety profile of intravenous tPA in stroke mimics.[4–13] While reported rates of thrombolysis-related complications are low, most of these studies were single center observations based on relatively small numbers of cases. Importantly, national quality improvement initiatives have focused on reducing treatment delays.[14] Despite compelling evidence of improved outcomes associated with shorter DTN times, there remain concerns that emphasis on minimizing DTN times may lead to a greater frequency of inadvertent administration of tPA to stroke mimics.[15] Therefore, the clinical consequences associated with thrombolysis administration to patients without ischemic stroke must be considered. Consequently, we examined intravenous tPA among patients hospitalized at the AHA/ASA Get With The Guidelines—Stroke (GWTG-Stroke) hospitals in the United States. Our specific goals were to identify factors associated with stroke mimics among suspected stroke patients treated with tPA and to evaluate the safety and outcomes of intravenous tPA in stroke mimics.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Data Source

The GWTG-Stroke is an ongoing, voluntary, national stroke registry and performance improvement program sponsored by the AHA/ASA. Details of the design and conduct of the GWTG-Stroke Registry have been previously described.[16, 17] Standardized data collection

includes patient demographics, medical history, diagnostic testing, brain imaging, in-hospital treatment and outcomes. The validity and reliability of data collection in the GWTG-Stroke has been reported in previous research.[18] IQVIA serves as the data collection and coordination center for GWTG-Stroke. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. The institutional review board of Duke University approved this study. Each participating hospital received either human research approval to enroll patients without individual patient consent under the Common Rule or a waiver of authorization and exemption from subsequent review by their institutional review board.

Study Population

Our analyses included suspected ischemic stroke patients receiving intravenous tPA in GWTG-Stroke hospitals between January 2010 and December 2017. Stroke mimic was defined as patients who present with stroke-like symptoms, but after work-up are determined not to have suffered from a stroke or transient ischemic attack (ruling out true positive at discharge). Hospitals have the option of recording the number of stroke mimics in the database, and if they do, the further option of recording the final non-stroke diagnosis, including migraine, seizure, delirium, electrolyte or metabolic imbalance, functional disorder, other (final clinical diagnosis is determined not to be stroke related, but the specific diagnosis is something other than those provided, or uncertain (final clinical diagnosis is determined not to be stroke related but the cause of the patient's symptoms is not confirmed or unknown at the time of discharge). We excluded patients transferred from another hospital, who had received tPA at an outside hospital, those undergoing investigational or experimental protocols for thrombolysis, or catheter-based reperfusion. Because hospitals submitting stroke mimic cases to the registry was encouraged but was optional, we further limited the analyses to hospitals that were submitting their mimic cases by requiring at least 10 intravenous tPA cases and 5 stroke mimics during the entire study period. After these exclusions, our primary study population consisted of 72,582 suspected stroke patients receiving intravenous tPA from 485 hospitals.

The primary safety outcomes were symptomatic intracranial hemorrhage (sICH), life-threatening or serious systemic hemorrhage, other serious complications, and a composite endpoint of any tPA complications. sICH was defined as intracerebral hemorrhage within 36 hours, as documented by computed tomography (CT) or magnetic resonance imaging (MRI) and the treating physician's notes indicating clinical deterioration attributable to hemorrhage.[19] Any tPA complications include sICH, life-threatening/serious systemic hemorrhage, or other serious complications. In-hospital outcomes include in-hospital mortality, discharge destination (home, hospice, skilled nursing facility [SNF], or inpatient rehabilitation facility [IRF]), and independent ambulation at discharge.

Statistical Analyses

Means, medians, and percentages were used to describe the distributions of continuous and categorical variables, respectively. Baseline characteristics were compared between tPA-treated stroke mimics and acute ischemic strokes by Wilcoxon rank-sum test for continuous variables and Pearson Chi-square test for categorical variables. Multivariable logistic

regression analyses were performed to investigate the relationships between stroke mimics vs. acute ischemic strokes and each clinical outcome. These analyses adjusted for baseline patient demographic and clinical factors as well as hospital characteristics that are expected to be predictive of outcome and have been used in prior GWTG-Stroke analyses.[19–24] Patient-level variables include age, sex, race/ethnicity, medical history of atrial fibrillation/flutter, previous stroke or transient ischemic attack (TIA), carotid stenosis, coronary artery disease, heart failure, hypertension, dyslipidemia, diabetes mellitus, peripheral vascular disease, smoking, arrival time during regular working hours (7AM to 6PM Monday through Friday), and baseline National Institutes of Health Stroke Scale (NIHSS, a measure of neurological deficits; range 0–42, with a higher score indicating greater stroke severity).[25] Hospital-level characteristics included hospital bed size, academic status, primary stroke center status, hospital region, annual ischemic stroke volume, and annual tPA volume.

To identify factors associated with stroke mimics, we ran a similar logistic regression model with final clinical diagnosis (stroke mimics vs. ischemic stroke) as the dependent variable, and the above-mentioned characteristics as independent variables. In addition, we added patient location when stroke symptoms discovered, arrival by emergency medical services (EMS), onset to arrival time, ambulatory status prior to current event, ambulatory status on admission, initial exam findings, systolic blood pressure, heart rate, and medication prior to admission in the model, because these variables are expected to be predictive of ischemic stroke or stroke mimic. We also included calendar year due to the greater concern of thrombolysis in stroke mimics in more recent years. Medical history missing was imputed to no, as we assume it was missing when none applied. Multiple imputation method using fully conditional specification with 25 independent datasets was used to impute missing data in other clinical characteristics. Missingness in hospital characteristics were not imputed. All these analyses accounted for within-hospital clustering using a generalized estimating equations approach.

All p-values are 2 sided, with $p<0.05$ considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). The institutional review board of Duke University approved the study.

Results

Characteristics and Etiologies of Stroke Mimics

Of 72,582 suspected stroke patients treated with intravenous tPA, 2,517 (3.5%) were classified as stroke mimics and 70,065 (96.5%) as true ischemic strokes. Table 1 shows the baseline demographic, clinical characteristics, and hospital characteristics between stroke mimics and true ischemic stroke. Compared with true ischemic stroke, mimic patients tended to be younger (median 54 years, interquartile range [IQR] 44–66 vs. 71, IQR 59–82), were more likely women, and more often had Medicaid insurance, were self-pay, or had no insurance. On initial presentation, patients with stroke mimic were less likely to present with weakness/paresis and aphasia, and had lower NIHSS scores (median 6, IQR 4–10 vs. 8, IQR 4–15), compared with true ischemic stroke patients. Additionally, stroke mimics patients were more likely able to ambulate independently upon admission. Also, they were more likely to experience longer time from “stroke symptom” onset to hospital arrival (median 66

minutes, IQR 41–107 vs. 62, IQR 41–100), and were less likely to arrive by EMS. Except for cigarette smoking and previous history of stroke and TIA, stroke mimic patients also had fewer comorbidities and vascular risk factors. Of 2,517 patients treated with tPA who were recorded as stroke mimics, 38.2% (962/2,517) had a final non-stroke diagnosis recorded, compromising 1.3% of all patients treated with tPA. The most common final non-stroke diagnoses were migraine (478/2,517, 19.0%), followed by functional disorder (236/2,517, 9.4%), seizure (199/2,517, 7.9%), electrolyte or metabolic imbalance (49/2,517, 2.0%), while the majority were either other/uncertain (979/2,517, 38.9%) or missing (564/2,517, 22.4%). Characteristics and outcomes of stroke mimics where the final non-stroke diagnosis was documented vs stroke mimics where the final non-stroke diagnosis was missing or unknown are shown in the Supplemental Table.

Factors Associated with Stroke Mimics

After multivariable adjustment, younger age, women, Medicaid insurance, history of previous stroke or TIA, presenting with altered states of consciousness, or receiving care at academic centers were all associated with an increased odds of stroke mimics (Table 2). Conversely, Hispanic, Asian race, history of atrial fibrillation, prosthetic heart valve, coronary artery disease, diabetes, hypertension, cigarette smoking, heart failure, symptom discovered in a healthcare facility, arriving by EMS, needing assistance or unable to ambulate on admission, presenting with weakness/paresis, or aphasia were associated with lower odds of stroke mimics. The relationship between hospital thrombolysis volume and thrombolysis in stroke mimics was complex. Hospitals with limited experience in stroke thrombolysis (≤30 cases per year) were more likely to give tPA to stroke mimics (adjusted odds ratio [OR] 1.16 per 5 cases increase, 95% confidence internal [CI] 1.11–1.20) until reaching a plateau of more than 30 tPA cases per year (adjusted OR 1.00 per 5 cases increase, 95% CI 0.99–1.01). Meanwhile, there was an overall trend of increasing tPA administration to stroke mimics in more recent years (adjusted OR 1.25 per year, 95% CI 1.22–1.28 from 2010 to 2017).

Safety and In-hospital Outcomes of Thrombolysis in Stroke Mimics

Of 2,517 stroke mimics treated with tPA, 11 patients had sICH (0.4%, Table 3). In comparison, 2,451 true ischemic strokes developed sICH (3.5%) after thrombolytic therapy. Meanwhile, there was only one case of life-threating or serious systemic hemorrhage in the stroke mimic cohort. The unadjusted rates of other serious complication and any tPA complications were 1.0% and 1.5% in stroke mimics, respectively, as compared with 2.8% and 6.9% in ischemic stroke. After risk adjustment, mimic patients were less likely to experience sICH (adjusted OR 0.29, 95% CI 0.17–0.50), life-threatening or serious systemic hemorrhage (adjusted OR 0.15, 95% CI 0.03–0.84), or any tPA complications after thrombolytic therapy (adjusted OR 0.48, 95% CI 0.36–0.64). Mortality rates were also lower in stroke mimics (0.8% vs. 6.2%; adjusted OR 0.31, 95% CI 0.20–0.49). In contrast, mimic patients were more likely to discharge home (83.8% vs. 49.3%; adjusted OR 2.97, 95% CI 2.59–3.42) and able to ambulate independently at discharge (78.6% vs. 50.6%; adjusted OR 1.86 95% CI 1.61–2.14).

Discussion

In this large cohort of patients treated with tPA, relatively few patients who received tPA for presumed stroke was ultimately not diagnosed with a stroke or TIA. The complication rates associated with tPA administration to stroke mimics were quite low (0.4% sICH compared with 3.5% in ischemic stroke, adjusted OR 0.29, 97% CI 0.17–0.50), suggesting that the possibility of stroke mimics should not preclude thrombolytic therapy in suspected stroke patients based on safety concerns. Considering that delaying tPA administration to gather more data for higher diagnostic certainty would worsen the chances of a good outcome for the approximate 96.5% of patients with true ischemia, the current health systems emphasis on rapidly administering tPA may be justified.

This study is the largest multi-center investigation of stroke mimics. Overall, we found 3.5% of tPA treatments were given to stroke mimics. If the estimate is restricted to patients with a specific non-stroke diagnosis recorded (e.g. migraine), which may be more specific, then the rate could be as low as 1.3%.While this figure is in the low range of previously reported studies from 1.4% to 15.5%, it should be noted that case report or single center studies often produce biased estimates due to publication bias.[4–10, 12, 13] Here, we observed that academic centers are more likely to give tPA to stroke mimics, which may reflect physicians' preference for reperfusion, even if the diagnosis is still uncertain. Interestingly, we found a complex relationship between hospital stroke thrombolytic volume and tPA use in stroke mimics, in which hospitals were more likely to give tPA to mimics when they had limited experiences with tPA administration, but no such differences once surpassing a threshold of 30 cases/year. Considering that tPA remains substantially underused in the United States and the median hospital tPA volume is only 14 cases/year even among GWTG-Stroke hospitals, [26] there are still opportunities to improve accurate diagnosis and timely tPA administration for patients with ischemic stroke.

There were multiple patient factors associated with increased odds of stroke mimics including younger age, female, Medicaid insurance, history of previous stroke or TIA, and presenting with altered states of consciousness. While these factors may be an area for future research to attempt to determine a screening system for stroke mimics, allowing this to play a role in current medical decision making may lead to the misdiagnosis and decrease in treatment of true ischemic stroke patients. This is especially true for some of the known stroke risk factors including previous stroke and TIA.

Treatment of ischemic stroke requires rapid decision-making as the efficacy time window for acute therapies is narrow, and outcomes are better with earlier treatment.[3] The strong emphasis now placed on reducing DTN times may lead to increased treatment of stroke mimics. Nonetheless, the low number of sICH in stroke mimics found in this study (0.4%) compared to true ischemic stroke (3.5%) as well as the lower overall complications from tPA (1.5% vs 6.9%) demonstrate the minimal risk of treating stroke mimic patients. While not directly comparable as patients with acute myocardial infarction (AMI) are often older, have more vascular risk factors, and get higher doses of tPA, the rate of sICH in stroke mimics is 60% lower than those from thrombolysis for AMI (0.4% vs. 1.0%).[27] Based on the low risk of treating mimics, Saver et al, concluded that the upper limit for the acceptable rate of tPA

in stroke mimics is 75%, meaning that a delayed strategy for more certain diagnosis would yield the same rate of harm in terms of reduced likelihood of good outcomes as long as a patient is 25% or more likely to have an ischemic stroke rather than a stroke mimic.[28] Importantly, faster treatment would also translate into more eligible stroke patients treated with tPA. Therefore, a small increase in the treatment of stroke mimics may represent a reasonable tradeoff for earlier treatment time of acute stroke patients and their subsequent improved outcomes.

This study has several limitations. First, our study is subject to potential reporting bias. Unlike ischemic stroke, the identification of stroke mimics relies on voluntary data reporting of “no stroke related diagnosis”. While the accuracy of stroke-related diagnosis has been reported in previous GWTG-Stroke data audit,[18] it remains unclear whether coding instruction have been followed for optional data elements such as “stroke mimics”. Additionally, there is no validated consensus definition of a stroke mimic. In the absence of a validated consensus definition of stroke mimics, the true rate of tPA-treated stroke mimics may be over or underestimated. For example, many mimic patients (60%) lacked a final non-stroke diagnosis reported in the registry, most likely because this data element was optional but also potentially reflecting clinical uncertainty or incomplete work up. This may lead to false positive diagnosis of stroke mimics and consequently overestimate the absolute event rates of mimics treated with tPA. Similarly, it is also conceivable that the number of treated mimics is underestimated. For example, patients with stroke mimics may not be reported in the registry or may receive a “TIA” diagnosis (which, itself has poor reliability) which may lead to an under-counting of the number of mimics. Second, we limited the analyses to hospitals with at least 10 tPA cases and 5 stroke mimics during the entire study period. While this approach helps maintain a more reliable estimate, there is also the potential for some selection bias as hospitals were included based on the number of tPA cases and stroke mimic cases, and consequently excluded small community hospitals with low volumes. Third, multiple imputations were performed for clinical characteristics with missing values. Depending on the missing rate, this method may introduce bias in variables that are not missing at random. Fourth, although our study represents the largest cohort of patients treated with intravenous tPA, this study does not address the important outstanding question on the clinical outcomes of stroke mimic cases treated with tPA compared with other stroke mimics not treated with tPA. Sixth, GWTG-Stroke is a voluntary program. Hospitals participated in this registry based on their level of interest in quality improvement in stroke care and their capacity to fulfill the requirements. Data from this registry and these study results might not be able to be extrapolated to patients treated in hospitals not participating in the registry or to patients in other countries.

Conclusions

In this large cohort of patients received tPA for presumed stroke, relatively few patients who received tPA for presumed stroke was ultimately not diagnosed with a stroke or TIA. The complication rates for stroke mimics were nominal and outcomes were favorable. These findings demonstrate that opportunities remain for continued improvement in the rapid and accurate diagnosis and treatment of ischemic stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures

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What is Known

- The necessity for rapid evaluation and treatment of acute ischemic stroke with intravenous tissue plasminogen activator (tPA) may increase the risk of administrating tPA to patients presenting with non-cerebrovascular conditions that closely resemble stroke (“stroke mimics”).
- There are limited data on thrombolysis safety in stroke mimics.

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What the Study Adds

- Relatively few patients who received tPA for presumed stroke was ultimately not diagnosed with a stroke or TIA in the Get With The Guidelines-Stroke Registry.
- The tPA-related complication rates for stroke mimics were nominal and outcomes were favorable.
- These findings demonstrate that opportunities remain for continued improvement in the rapid and accurate diagnosis and treatment of ischemic stroke.

Table 1.

Characteristics of Stroke Mimics and Acute Ischemic Strokes Treated with Intravenous Tissue Plasminogen Activator (tPA)

Variable	Stroke Mimics N=2517	Ischemic Stroke N=70065	p-value
Demographics			
Age, median (IQR), y	54 (44–66)	71 (59–82)	<0.001
Female, No. (%)	1545 (61.4)	34,943 (49.9)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	1423 (56.5)	46,828 (66.8)	
Non-Hispanic black	613 (24.4)	11,901 (17.0)	
Hispanic	243 (9.7)	5644 (8.1)	
Asian	58 (2.3)	2267 (3.2)	
Other	163 (6.5)	3266 (4.7)	
Insurance			<0.001
Private	1055 (42.0)	27,911 (39.8)	
Medicare	432 (17.2)	21,577 (30.8)	
Medicaid	442 (17.6)	6634 (9.5)	
Self-pay	205 (8.1)	3578 (5.1)	
Medical history			
Atrial fibrillation/flutter	86 (3.4)	13,343 (19.0)	<0.001
Prosthetic heart valve	9 (0.4)	692 (1.0)	0.003
Previous stroke/transient ischemic attack	787 (31.3)	18,312 (26.1)	<0.001
Carotid stenosis	35 (1.4)	1701 (2.4)	0.004
Coronary artery disease/prior myocardial infarction	324 (12.9)	15,913 (22.7)	<0.001
Heart failure	101 (4.0)	6249 (8.9)	<0.001
Hypertension	1392 (55.3)	50,661 (72.3)	<0.001
Dyslipidemia	820 (32.6)	29,049 (41.5)	<0.001
Peripheral vascular disease	42 (1.7)	2197 (3.1)	<0.001
Diabetes mellitus	669 (26.6)	19,725 (28.2)	0.72
Smoker	518 (20.6)	11,932 (17.0)	<0.001
Clinical characteristics			
Arrival by emergency medical services (EMS)	1554 (61.7)	54,267 (77.5)	<0.001
Off-hour admission*	1174 (46.6)	34,092 (48.7)	0.05
Patient location when stroke symptoms discovered, healthcare facility	130 (5.2)	4150 (6.0)	<0.001
Onset to arrival time, median (IQR), minutes	66 (41–107)	62 (41–100)	0.01
Ambulatory status prior to current event, with assistance/unable to ambulate†	89 (3.5)	3311 (4.7)	0.02
Ambulatory status on admission, with assistance/unable to ambulate‡	731 (29.0)	29177 (41.6)	<0.001
Initial exam findings			
No neurological signs/symptoms	10 (0.4)	127 (0.2)	0.01
Weakness/paresis	1411 (56.1)	44,139 (63.0)	<0.001
Altered states of consciousness	383 (15.2)	11,133 (15.9)	0.81

Variable	Stroke Mimics N=2517	Ischemic Stroke N=70065	p-value
Aphasia	915 (36.4)	32,356 (46.2)	<0.001
Other neurological signs/symptoms	689 (27.4)	14,559 (20.8)	<0.001
National Institutes of Health Stroke Scale (NIHSS)			<0.001
Mean (SD)	8.0 (6.0)	10.1 (7.4)	
Median (IQR)	6 (4–10)	8 (4–15)	
Systolic blood pressure, median (IQR), mmHg	147 (131–167)	155 (138–176)	<0.001
Heart rate, median (IQR), bpm	84 (73–96)	80 (70–93)	<0.001
Door-to-needle time, median (IQR), min	56 (43–77)	54 (41–72)	<0.001
Medications prior to admission			
Antiplatelets or anticoagulants	912 (36.2)	33,511 (47.8)	<0.001
Antihypertensive	1116 (44.3)	39,819 (56.8)	<0.001
Cholesterol reducer	819 (32.5)	29,535 (42.2)	<0.001
Diabetic medication	495 (19.7)	12,696 (18.1)	0.10
Hospital characteristics			
Number of beds, median (IQR)	493 (310–695)	427 (290–663)	<0.001
Annual ischemic stroke volume, median (IQR)	257 (202–409)	267 (201–415)	0.25
Hospital type, academic	2109 (83.8)	57,516 (82.1)	0.08
Primary stroke center	1701 (67.6)	47,340 (67.6)	0.99
Annual IV tPA cases, median (IQR)	35 (25–49)	33 (22–45)	<0.001
Rural	24 (1.0)	1059 (1.5)	0.02
Geographic region			<0.001
Northeast	512 (20.3)	16,684 (23.8)	
Midwest	364 (14.5)	11,262 (16.1)	
South	931 (37.0)	24,678 (35.2)	
West	710 (28.2)	17,441 (24.9)	
Calendar year			<0.001
2010	48 (1.9)	4731 (6.8)	
2011	64 (2.5)	5644 (8.1)	
2012	134 (5.3)	6775 (9.7)	
2013	195 (7.8)	8335 (11.9)	
2014	268 (10.7)	9262 (13.2)	
2015	373 (14.8)	10,515 (15.0)	
2016	695 (27.6)	12,002 (17.1)	
2017	740 (29.4)	12,801 (18.3)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*Off-hour presentation, presentation anytime outside of 7am to 6pm on weekdays

†Ambulatory status prior to admission: 26.2% missing in stroke mimics and 25.6% missing in ischemic stroke

‡Ambulatory status on admission: 49.3% missing in stroke mimics and 43.5% missing in ischemic stroke

Table 2.

Factors Associated with Stroke Mimics among Patients Receiving Intravenous Tissue Plasminogen Activator (tPA)

Variable	Adjusted OR and 95% CI
Demographics	
Age, per 10-year increase	0.61 (0.59–0.63)
Female	1.75 (1.60–1.91)
Race/ethnicity	
Non-Hispanic white	Reference
Non-Hispanic black	1.09 (0.98–1.22)
Hispanic	0.83 (0.71–0.97)
Asian	0.70 (0.53–0.92)
Other	1.12 (0.93–1.34)
Insurance	
Private	Reference
Medicaid	1.40 (1.23–1.59)
Medicare	1.12 (0.99–1.26)
Self-pay	1.11 (0.94–1.31)
Medical history	
Atrial fibrillation/flutter	0.33 (0.27–0.42)
Prosthetic heart valve	0.44 (0.22–0.86)
Previous stroke/transient ischemic attack	1.47 (1.33–1.62)
Coronary artery disease/prior myocardial infarction	0.86 (0.76–0.99)
Carotid stenosis	0.92 (0.64–1.31)
Diabetes mellitus	0.84 (0.73–0.98)
Peripheral vascular disease	0.86 (0.62–1.19)
Hypertension	0.73 (0.65–0.82)
Smoker	0.84 (0.75–0.93)
Dyslipidemia	1.04 (0.93–1.15)
Heart failure	0.65 (0.52–0.81)
Clinical characteristics	
Patient location when stroke symptoms discovered, healthcare facility	0.62(0.51–0.76)
Arrival by emergency medical services (EMS)	0.79 (0.71–0.87)
Off-hour admission *	0.95 (0.87–1.03)
Onset to arrival time, per 10 minutes increase	1.01 (1.00–1.01)
Ambulatory status prior to current event, with assistance/unable to ambulate	1.19 (0.93–1.51)
Ambulatory status on admission, with assistance/unable to ambulate	0.86 (0.76–0.98)
Initial exam findings	
Weakness/paresis	0.63 (0.56–0.72)
Altered states of consciousness	1.56 (1.37–1.77)
Aphasia	0.72 (0.64–0.80)
Other neurological signs/symptoms	1.05 (0.94–1.16)

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Variable	Adjusted OR and 95% CI
No neurological signs/symptoms	Reference
National Institutes of Health Stroke Scale, per 5 points increase	1.00 (0.96–1.05)
Systolic blood pressure, per 10 mmHg increase	
≤130	1.00 (0.94–1.07)
131–180	0.92 (0.89–0.95)
>180	1.05 (1.00–1.11)
Heart rate, per 10 bpm increase	1.02 (0.99–1.05)
Medications prior to admission	
Antiplatelets or anticoagulants	1.00 (0.90–1.11)
Antihypertensive	1.18 (1.05–1.32)
Cholesterol reducer	0.91 (0.81–1.02)
Diabetic medication	1.45 (1.23–1.71)
Hospital characteristics	
Hospital type, academic	1.18 (1.04–1.34)
Rural	0.78 (0.50–1.22)
Geographic region	
Northeast	Reference
Midwest	0.90 (0.78–1.05)
South	0.97 (0.86–1.10)
West	1.22 (1.06–1.40)
Hospital size, per 50 beds increase	0.99 (0.98–1.00)
Primary stroke center	0.94 (0.86–1.04)
Annual IV tPA cases, per 5 cases increase	
≤30	1.16 (1.11–1.20)
>30	1.00 (0.98–1.01)
Calendar year, per one-year increase from 2010 to 2017	1.25 (1.22–1.28)

* Off-hour presentation, presentation anytime outside of 7am to 6pm on weekdays

Table 3.

Safety Endpoints and In-hospital Outcomes After Intravenous Tissue Plasminogen Activator in Stroke Mimics and Acute Ischemic Stroke

	Stroke Mimics N=2517	Ischemic Stroke N=70,065	Adjusted OR (95% CI)	p-value
Safety endpoints				
Symptomatic intracranial hemorrhage	11 (0.4)	2451 (3.5)	0.29 (0.17–0.50)	<0.001
Life-threatening or serious systemic hemorrhage	1 (0)	516 (0.7)	0.15 (0.03–0.84)	0.03
Other serious complication	26 (1.0)	1938 (2.8)	0.73 (0.51–1.03)	0.08
Any tPA complication *	38 (1.5)	4803 (6.9)	0.48 (0.36–0.64)	<0.001
In-hospital outcomes				
In-hospital mortality	21 (0.8)	4324 (6.2)	0.31 (0.20–0.49)	<0.001
Discharge to home	2109 (83.8)	34,511 (49.3)	2.97 (2.59–3.42)	<0.001
Discharge to hospice	16 (0.6)	3401 (4.9)	0.39 (0.23–0.69)	0.001
Discharge to SNF	189 (7.5)	10,379 (14.8)	1.00 (0.86–1.16)	0.98
Discharge to IRF	157 (6.2)	16,256 (23.2)	0.26 (0.22–0.32)	<0.001
Independent ambulation at discharge †	1542 (78.6)	31,277 (50.6)	1.86 (1.61–2.14)	<0.001

IRF, inpatient rehabilitation facility; SNF, skilled nursing facility.

*A composite measure of symptomatic intracranial hemorrhage<36 hours, life threatening or serious systemic hemorrhage<36 hours, or other serious complications.

†Exclude missing values