The Association between t-PA Administration and In-Hospital Mortality following Acute Ischemic Stroke in Puerto Rican Patients

Kevin Shah, BS*; Samuel Kohrman, BS*; Suehyb Alkhatib, MS*; Juan González, MD†; Fernando Santiago, MD†; Marcia Varella, MD, PhD*; Juan Zevallos, MD*

Objective: Despite being the standard of care, thrombolytic therapy with tissue plasminogen activator (t-PA) is currently administered to only 5% of acute ischemic stroke (AIS) patients in the United States. Published scientific information regarding both the use of t-PA for AIS in Hispanic patients and its impact on short-term mortality is scarce. The objectives of this study are to investigate, among Puerto Rican patients hospitalized with AIS, the rate of t-PA administration, and the risk of in-hospital mortality in patients who received t-PA vs. those patients who did not receive t-PA.

Methods: We performed a secondary analysis of data from patients with AIS admitted to acute care facilities throughout Puerto Rico in study years 2007, 2009, and 2011who were participating in the Puerto Rico Cardiovascular Disease Surveillance System. Multivariate logistic regression was used to determine the independent association between treatment with t-PA within 4.5 hours of symptom onset and in-hospital mortality.

Results: Of the 1968 study patients hospitalized with AIS, 104 (5%) received t-PA treatment. After adjustments for demographic and clinical confounders, patients receiving t-PA had similar odds of in-hospital mortality as patients not receiving t-PA did (OR = 2.49, 95% CI = 0.81–7.66). The receipt of concomitant anticoagulation medication was independently associated with relatively lower odds of in-hospital mortality (OR = 0.42, 95% CI = 0.20–0.88). Being over 80 years of age (OR = 2.03, 95% CI = 1.13–3.68), being obese (OR = 1.88, 95% CI = 1.01–3.49), and arriving in an ambulance (OR = 3.61, 95% CI = 1.95–6.68) were all independently associated with relatively higher odds of in-hospital mortality.

Conclusion: Among patients hospitalized in Puerto Rico with acute ischemic stroke, t-PA treatment was not significantly associated with in-hospital mortality. [*P R Health Sci J 2016;35:215-219*]

Key words: Acute Ischemic Stroke, t-PA, Tissue Plasminogen Activator, Thrombolytics, In-Hospital Mortality

Acute ischemic stroke (AIS) remains a significant cause of mortality and morbidity worldwide (1). In the United States, approximately 130,000 individuals die each year from acute strokes (2), and approximately one third of acute stroke patients develop disabilities as a result of their strokes (3).

Several randomized controlled studies have evaluated the effectiveness of early intravenous tissue plasminogen activator (t-PA) treatment at improving stroke symptoms while also reducing both disability and mortality. The results of several AIS follow-up meta-analyses have also suggested that intravenous t-PA therapy improves survival and quality of life (4–8).

Since receiving the Food and Drug Administration's (FDA) approval in 1996, thrombolytic therapy with t-PA has become accepted as the most effective intervention in terms of limiting ischemic tissue damage in AIS patients (9) and is considered the standard of care for AIS. Yet, despite these advances, the proportion of AIS patients treated with t-PA is still low, while stroke mortality remains high (1, 5). Possible explanations for those findings include the narrow time window (within 4.5 hours of symptom onset) in which thrombolytic therapy must be initiated and the higher risks of both symptomatic intracerebral hemorrhage (ICH) and short-term death associated with thrombolytic therapy administration (9–12). Finally, there is conflicting evidence regarding t-PA's benefit in terms of its reducing overall mortality in different populations (13–15).

*Herbert Wertheim College of Medicine, Florida International University, Miami, Florida; †University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

The authors have no conflicts of interest to disclose.

Address correspondence to: Kevin Shah, Herbert Wertheim College of Medicine, Florida International University, 11200 SW 8th Street, AHC 2, Miami, Florida 33199. Email: kshah011@fiu.edu

The prevalence of stroke in Puerto Rico (1.9%) is slightly lower than the overall prevalence of stroke in the United States (2.6%) (1). However, very few studies have reported on the rate of t-PA administration and its impact on in-hospital mortality (IHM) in patients hospitalized in Puerto Rico (16). For that reason, we aimed to determine the following in AIS patients hospitalized in Puerto Rico: 1) the rate of t-PA treatment; 2) the effect of t-PA treatment on IHM; and 3) the explanatory variables for the association between t-PA administration and IHM risk.

Methods

Study design

We performed a secondary analysis of the data from patients of the Puerto Rico Cardiovascular Disease Surveillance System (PRCDSS), which has a non-concurrent prospective study design.

Population and Database description

Puerto Ricans are mostly Hispanics. The PRCDSS collected information about adult (18 years old and older) patients living in Puerto Rico, who had been hospitalized with acute myocardial infarction, heart failure, or stroke. This study included only PRCDSS patients with AIS. The data collection for the PRCDSS followed an adapted standardization of methods developed for the Worcester Heart Attack Study (17). An electronic database was established to collect data from the medical records of patients with ICD-9 codes 434 (occlusion of cerebral artery) and 436 (acute but ill-defined cerebrovascular disease), as reported by a total of 21 medical centers with acute care facilities in the years of 2007, 2009, and 2011. Only the records of patients with an AIS diagnosis validated by CT or MRI and of patients admitted with an initial acute stroke during the 3 study years were included. Patients with transient cerebral ischemia (ICD-9 code 435.9) were excluded.

The collected patient information included demographics, medical history, and clinical symptomatology on presentation as well as physical exam findings, mode of transportation to the hospital, treatment administered, and IHM.

Variables

The independent variable was the administration of t-PA within 4.5 hours of symptom onset. The dependent variable was IHM as reported by the discharge status in the medical records. Patient information regarding comorbidities including obesity (defined as a BMI ≥ 30 Kg/m2), dyslipidemia, diabetes, hypertension, atrial fibrillation, smoking status, hospital arrival mode, demographics (including gender and age), concomitant anticoagulant medications, and symptomatic ICH were also analyzed for their potential roles as confounders. The definitions of these variables are listed in Appendix A.

Data analysis

We performed a preliminary exploratory data analysis to identify outliers and patterns of missing data. Subsequently we evaluated the crude proportion of IHM in patients who had received t-PA. We then conducted a bivariate analyses to test the association of potential confounding variables with IHM. Statistical differences between categorical variables were tested using chi-square statistics. Lastly, we used multivariate logistic regression models to evaluate the independent association between t-PA administration and IHM. To test the desired level of independence and to select the correct variables (adequacy), we evaluated a parsimonious model including variables associated with both dependent and independent variables in our sample (Model 1) (18), as well as variables of clinical relevance reported in the published literature (Model 2). P-values less than 0.05 were considered for statistical significance for a 2-tailed test. Analyses were performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY: IBM Corp.) (19). The Institutional Review Boards of Florida International University and University of Puerto Rico Medical Sciences Campus approved this study.

Results

A total of 1968 patients were admitted to 21 hospitals in Puerto Rico in 2007, 2009, and 2011—each with a CT- or MRI-confirmed diagnosis of AIS—and were included in this study. Of these, 104 (5%) patients received t-PA treatment. Eighty-five patients died during their stay in the hospital: 80 (4%) of those in the non–t-PA group and 5 (5%) of those in the t-PA group (Table 1). Twelve (60%) hospitals were considered to be "academic," according to the Association of American Medical Colleges definition of "teaching status" (20).

Overall, 71% of the patients were younger than 79 years old, 52% were women, and 18% were obese. Hypertension was the most common comorbidity, affecting 95% of patients, followed by hyperlipidemia (62%) and diabetes mellitus (55%). About 9% of the sample patients were current smokers, 5% had reported excessive alcohol use, and 85% were currently taking anticoagulation medication. Women received significantly less t-PA than did their male counterparts ($p = 0.004$). Of all patients, those who received t-PA were significantly less likely to have hypertension ($p = 0.016$) than were those who did not (Table 1).

An additional analysis conducted with a similar number of patients (N = 110) not receiving t-PA and paired by gender, age, and selected comorbidities (along with having had t-PA administered within 4.5 hours of the onset of symptoms) showed results similar to those of the original analysis with 1864 patients indicated in Table 1 (data not shown).

Table 2 shows the results of the multivariate analysis. In Model 1, we only adjusted for patient gender and history of excessive alcohol use. In addition to patient gender and history of excessive alcohol use, in Model 2 we further adjusted for BMI, history of hypertension, presence of hyperlipidemia, presence of diabetes, concomitant use of anticoagulant medication, presence of atrial fibrillation, smoking status, mode of arrival at the hospital, radiologic imaging method used for diagnosis, and presence of intra-cranial hemorrhage. In these patients, the receipt of t-PA

Table 1. Characteristics of stroke patients in the Puerto Rico Cardiovascular Disease Surveillance System who were treated with t-PA

Variable	t-PA administered		Total (N)	p-value
	% Yes (N = 104)	% No (N = 1864)		
In-hospital mortality (IHM)	4.80	4.30	85	0.803
Age ≥80[1]	29.80	29.10	569	0.885
Gender (being a woman)	35.50	52.90	1017	0.004
Obese BMI (kg/m^2)[2]	18.40	24.30	357	0.246
Diabetes mellitus	54.10	55.50	937	0.801
Current smoker	11.60	9.30	167	0.455
Alcoholism/excessive alcohol use*	2.30	6.5	102	0.116
EMS/ambulance[3]	46.90	44.10	821	0.586
ICH	10.00	2.30	41	0.722
Atrial fibrillation	7.10	8.00	130	0.787
Hyperlipidemia	65.90	61.90	1036	0.455
Hypertension	89.50	95.10*	1741	0.016
Anticoagulation	78.80	85.50	1658	0.063

t-PA = tissue plasminogen activator; BMI = body mass index; EMS = emergency medical services; ICH = intracerebral hemorrhage; 1 – Reference age group was <80 years of age; 2 – Non-obese includes overweight, normal weight, and underweight patients (by BMI); 3 – Reference was using personal car or walking in. *Alcoholism/excessive alcohol use: if "excess alcohol use/heavy drinking/alcohol use disorder/alcohol abuse" was ever mentioned in the medical history.

Table 2. Adjusted multivariate analysis identifying odds of in-hospital mortality in the Puerto Rico Cardiovascular Disease Surveillance System for all potential confounding variables for stroke outcomes

	In-hospital mortality (IHM)			
	Model 1		Model 2	
	OR	95% CI	OR	95% CI
t-PA administered	1.26	0.49 – 3.23	2.49	0.81 – 7.66
Gender (being a woman)	1.65	1.03 – 2.64	1.76	0.91 – 3.39
Alcoholism/excessive alcohol use*	0.45	0.11 – 1.87	0.82	0.18 – 3.72
Age ≥80[1]			2.03	1.13 – 3.68
Obese BMI (Kg/m^2)[2]			1.88	1.01 – 3.49
Diabetes mellitus			1.05	0.60 – 1.85
Current smoker			0.76	0.22 – 2.67
MRI[3]			1.16	0.63 – 2.12
EMS/ambulance[4]			3.61	1.95 – 6.68
ICH			0.86	0.10 – 7.26
Atrial fibrillation			1.44	0.60 – 3.48
Hyperlipidemia			0.78	0.44 – 1.39
Hypertension			3.28	0.42 – 25.61
Anticoagulation			0.41	0.20 – 0.88

t-PA = tissue plasminogen activator; BMI = body mass index; EMS = emergency medical services; ICH = intracerebral hemorrhage. 1 – Reference age group was <80 years of age; 2 – Non-obese includes overweight, normal weight, and underweight patients (by BMI); 3 – Reference imaging modality was CT; 4 – Reference was using personal car or walking in. *Alcoholism/excessive alcohol use: if "excess alcohol use/heavy drinking/alcohol use disorder/alcohol abuse" was ever mentioned in the medical history.

was not significantly associated with IHM (OR = 1.26, 95% CI = 0.49–3.23 and OR = 2.49, 95% CI = 0.81–7.66 in Models 1 and 2, respectively) (Table 2). In the adjusted analysis, women no longer had increased odds for IHM (OR 1.76, 95% CI = 0.91–3.39) and patients with hyperlipidemia did not have decreased odds for IHM (OR 0.78, CI = 0.44–1.39). However, other variables were found to be independently associated with IHM; notably, patients receiving concomitant anticoagulation were 58% less likely to die (OR = 0.42, 95% CI = 0.20–0.88), while age (>80 years) (OR = 2.03, 95% CI = 1.13–3.68), obesity (OR = 1.88, 95% CI = 1.01–3.49), and mode of arrival (by ambulance as opposed to walking in or arriving in a car or other kind of vehicle) OR = 3.61, 95% CI = 1.95–6.68) increased the odds of IHM.

Discussion

We found no evidence for an association between the receipt of t-PA and IHM in patients of the PRCDSS.

Many randomized controlled trials have evaluated the ability of intravenous t-PA to reduce overall mortality in patients with AIS, albeit with varying results, as detailed in the meta-analysis by Wardlow et al. (5). Yet, few studies have analyzed the risk of IHM associated with intravenous t-PA use, and fewer still have done so in a predominantly Hispanic population. Our results of short-term mortality compare with those from the trial by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (9), in which mortality throughout the 90 days of follow-up did not differ between groups treated with t-PA and those not so treated.

Several patient characteristics were found independently associated with IHM. Patients who received concomitant anticoagulation therapy demonstrated 58% lower odds of dying before being discharged, while patients of advanced age, who suffered from obesity, and whose mode of arrival at the hospital was an ambulance exhibited higher odds of dying before being discharged. A potential mechanism explaining the lower odds of IHM among patients receiving concomitant anticoagulants is that these patients might suffer less severe ischemic strokes compared to patients not receiving concomitant anticoagulants. Such a mechanism is supported by the scientific literature (21). For example, evidence supports the assertion that warfarin alone, even at sub-therapeutic dosages, decreases the initial stroke severity and the risk of re-occlusion after t-PA therapy (22, 23). In contrast, other studies have reported no association between any concomitant anticoagulation medication and IHM. An observational study which included 23,487 patients from the American Heart Association Get With The Guidelines-Stroke Registry, found that mortality in patients after intravenous t-PA treatment was not significantly different between the warfarin-treated and non-warfarin-treated groups (OR = 0.94, 95% CI = 0.79–1.13) (21). In a similar study of 1,739 patients in Canada, Vergouwen et al. reported that the preadmission use of warfarin was not associated with IHM (OR = 0.6, 95% CI = 0.3–1.0) (24). It must be noted that these studies included only patients treated with sub-therapeutic doses of warfarin (International Standardized Ratio<1.7), while our current analysis includes those patients treated with any dose of warfarin. Therefore, in our sample we might have higher rates of patients with therapeutic doses of anticoagulants, which could explain the presence of an association and the discrepancy between the two studies' results. Such factors merit future investigation.

Advanced age was also found to be associated with a twofold increased rate of IHM, which is consistent with previous reports. Kammersgaard, in a review of the Copenhagen Stroke Study, found age to be the most significant risk factor affecting short- and long-term post-stroke survival (25). Similarly, in a study analyzing the impact of the time of hospital admission on stroke outcomes involving 907 patients in Germany, older age (OR = 1.05 per year increase, 95% CI = 1.004–1.09) was associated with increased short-term mortality in t-PA–treated patients (26). Additionally, in a recent retrospective observational study of the Nationwide Inpatient Sample, a greater than twofold increase in IHM was reported in patients over 80 years old compared to their younger counterparts (27).

Regarding the independent association of obesity with IHM, most evidence suggests that increased body weight is associated with greater mortality in stroke patients (28-31). Our results were similar, showing that obesity was associated with an almost twofold increase in the odds of IHM.

In our study, patients who arrived at the hospital by ambulance were 3.7 times more likely to die before being discharged, which is contradictory to findings currently reported in the scientific literature (5, 32). There are few potential explanations for this fact: more severe AIS cases may arrive by ambulance; the emergency medical services (EMS) team might be responding in an untimely manner; or a potential lack in the geographical coverage of the local EMS provider may play a role. Unfortunately, the information available in the PRCDSS database is not sufficient for the testing of any of these hypotheses.

The PRCDSS is the first ongoing surveillance effort conducted in Puerto Rico whose aim is to systematically evaluate the therapeutic management and outcomes of patients hospitalized with AIS. Findings from this study contribute to the growing literature on t-PA treatment for AIS by providing evidence collected from a mostly Hispanic population. However, our finding that there is no association between t-PA treatment and IHM should be interpreted with caution: We had no data on either stroke severity or the interval between symptom onset and treatment time. Thus, we cannot rule out the possibility that these potential discrepancies between the different t-PA treatment groups were responsible for the lack of association (per our study) between t-PA treatment and IHM.

In conclusion, we found evidence that intravenous t-PA therapy was not associated with the risk of IHM in patients with AIS in Puerto Rico. While our findings suggest that t-PA is an intervention that may not lead to an increase in short-term mortality, further studies exploring the risks of disability and long-term mortality in the Puerto Rican AIS population are warranted to provide further evidence for the overall efficacy and safety of t-PA. Future studies might help provide further support to programs aimed at increasing the awareness of the efficacy and safety of t-PA among both medical providers and the public, ultimately improving the quality of health care for AIS patients.

Resumen

Objetivo: No obstante el tratamiento estándar para ataques cerebrales isquémicos (ACI) en Estados Unidos es la terapia trombolítica, el activador tisular de plasminógeno (t-PA, por sus siglas en inglés) se administra sólo en 5% de los casos. La información científica publicada es escasa, especialmente en pacientes hispanos, sobre el impacto de t-PA en mortalidad de corto plazo. Los objetivos de este estudio son investigar la tasa de administración de t-PA en pacientes con ACI en Puerto Rico y comparar la mortalidad hospitalaria y sus covariables respecto a la administración de t-PA. Métodos: Realizamos un análisis secundario de datos de pacientes hospitalizados con ACI en centros médicos con servicios de emergencia registrados en el Sistema de Vigilancia de Enfermedades Cardiovasculares de Puerto Rico durante 2007, 2009 y 2011. Usamos análisis logístico multivariado para determinar la independencia de la asociación entre mortalidad hospitalaria y tratamiento con t-PA dentro de 4.5h del inicio de síntomas. Resultados: De los 1968 pacientes hospitalizados con ACI, 104 (5%) recibió t-PA. Luego de realizar los ajustes demográficos y confusores clínicos, los pacientes que recibieron t-PA tuvieron chanzas similares de mortalidad hospitalaria que pacientes que no recibieron t-PA (OR=2.49, 95% IC=0.81-7.66). La administración de anticoagulación concomitante estuvo asociada independientemente con menor mortalidad hospitalaria (OR=0.42, IC 95%=0.20-0.88). Pacientes >80 años (OR=2.03, IC 95%=1.13-3.68), pacientes obesos (OR=1.88, IC 95%=1.01-3.49) y aquellos que arribaron en ambulancia (OR=3.61, IC 95%=1.95-6.68) estuvieron independientemente asociados con mayor mortalidad hospitalaria. Conclusión: En pacientes hospitalizados por ACI en Puerto Rico, el tratamiento con t-PA no estuvo asociado con mayor mortalidad hospitalaria.

Acknowledgments

We are sincerely grateful to Gretel Castro, MPH, and Pura Rodriguez de la Vega, MPH, from the Department of Medical and Health Sciences Research, Florida International University Herbert Wertheim College of Medicine, for the biostatistics support and assistance.

References

1. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol 2016;15:913–24.
2. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. Natl Vital Stat Rep 2016;64:1–119.
3. Khandelwal P, Yavagal DR, Sacco RL. Acute Ischemic Stroke Intervention. J Am Coll Cardiol 2016;67:2631–44.
4. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. In: Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 1996.
5. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke an updated systematic review and meta-analysis. Lancet 2012;379:2364–72.

6. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017–25.
7. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. Stroke 2002;33:493–5.
8. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA 2015;313:1451–62.
9. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–7.
10. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke 2011;42:1952–5.
11. Schwamm LH, Ali SF, Reeves MJ, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. Circ Cardiovasc Qual Outcomes 2013;6:543–9.
12. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317–29.
13. Nasr DM, Brinjikji W, Cloft HJ, Rabinstein AA. Racial and ethnic disparities in the use of intravenous recombinant tissue plasminogen activator and outcomes for acute ischemic stroke. J Stroke Cerebrovasc Dis 2013;22:154–60.
14. Park SJ, Shin SD, Ro YS, Song KJ, Oh J. Gender differences in emergency stroke care and hospital outcome in acute ischemic stroke: a multicenter observational study. Am J Emerg Med 2013;31:178–84.
15. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695–703.
16. Zevallos JC, Gonzalez J, Santiago F, et al. Pilot study of the characteristics of acute stroke events in patients discharged from the Carolina University Hospital, Puerto Rico in 2007. Bol Asoc Med P R 2009;101:11–3.
17. Goldberg RJ, Spencer FA, Yarzebski J, et al. A 25-year perspective into the changing landscape of patients hospitalized with acute myocardial infarction (the Worcester Heart Attack Study). Am J Cardiol 2004;94:1373–8.
18. Osborne NH, Ko YC, Upchurch GR Jr, Dimick JB. Evaluating parsimonious risk-adjustment models for comparing hospital outcomes with vascular surgery. J Vasc Surg 2010;52:400–5.
19. IBM Corp. IBM SPSS Statistics for Windows. Version 20.0. Armonk, NY: IBM Corp; 2011.
20. American Medical Association Council. Available at: https://www.aamc.org/. Accessed August 1, 2016.
21. Xian Y, Liang L, Smith EE, et al. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. JAMA 2012;307:2600–8.
22. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019–26.
23. Stroke Performance Measures. Centers for Disease Control: Division for Heart Disease and Stroke Prevention. Stroke performance measures. Available at: http://www.cdc.gov/dhdsp/. Accessed July 5, 2015.
24. Vergouwen MDI, Casaubon LK, Swartz, et al.; Investigators of the Registry of the Canadian Stroke Network. Subtherapeutic warfarin is not associated with increased hemorrhage rates in ischemic strokes treated with tissue plasminogen activator. Stroke 2011;42:1041–5.
25. Kammersgaard LP. Survival after stroke. Risk factors and determinants in the Copenhagen Stroke Study. Dan Med Bull 2010;57:B4189.
26. Haeusler KG, Gerischer LM, Vatankhah B, Audebert HJ, Nolte CH. Impact of hospital admission during nonworking hours on patient outcomes after thrombolysis for stroke. Stroke 2011;42:2521–5.
27. Nasr DM, Brinjikji W, Cloft HJ, Rabinstein AA. Utilization of intravenous thrombolysis is increasing in the United States. Int J Stroke 2013;8:681–8.
28. Sarikaya H, Elmas F, Arnold M, Georgiadis D, Baumgartner RW. Impact of obesity on stroke outcome after intravenous thrombolysis. Stroke 2011;42:2330–2.
29. Lou M, Selim M. Does body weight influence the response to intravenous tissue plasminogen activator in stroke patients? Cerebrovasc Dis 2009;27:84–90.
30. Towfighi A, Ovbiagele B. The impact of body mass index on mortality after stroke. Stroke 2009;40:2704–8.
31. Hassan AE, Chaudhry SA, Jani V, et al. Is there a decreased risk of intracerebral hemorrhage and mortality in obese patients treated with intravenous thrombolysis in acute ischemic stroke? J Stroke Cerebrovasc Dis 2013;22:545–9.
32. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013;309:2480–8.

Appendix A

Variable	Definition
t-PA administration	Defined as the receipt of any dose of t-PA within 4.5 hours of onset of AIS symptoms
In-hospital mortality	Defined as death before discharge from medical center; obesity defined as a body mass index ≥ 30 kg/m^2
Dyslipidemia	Individuals were identified as having dyslipidemia if they mentioned before admission and/or use of lipid-lowering agents during hospitalization and/or discharge
Diabetes	Individuals were identified as having diabetes mellitus (regardless of type) if mentioned before admission and/or use of hypoglycemic/insulin before admission, during hospitalization, and/or discharge
Hypertension	Individuals were identified as hypertensive if mentioned before admission and/or use of antihypertensive drugs during hospitalization and/or discharge
Atrial fibrillation	Individuals were identified as having atrial fibrillation if mentioned before admission and/or occurred during hospitalization and/or at discharge
Smoking status	Defined as currently smoking or not currently smoking
Hospital arrival mode	Defined by emergency medical service/ambulance or by taxi/private vehicle
Gender	Defined as man or woman
Age	Individuals were grouped into the following age groups: ≤ 79 years old and ≥ 80 years old
Concomitant anti-coagulant medication	Individuals were identified as taking concomitant anti-coagulant medication if warfarin was used during hospitalization
Symptomatic intracerebral hemorrhage	Defined as the diagnosis of ICD-9 code 432 and verified by imaging
Alcoholism/Excessive alcohol use	Individuals were identified as using excessive amounts of alcohol if any of the following phrases were used in their medical charts: excess alcohol use/heavy drinking/alcohol use disorder/alcohol abuse.