Comorbid Psychiatric Disease Is Associated With Lower Rates of Thrombolysis in Ischemic Stroke

Diana M. Bongiorno, BA, BS; Gail L. Daumit, MD, MHS; Rebecca F. Gottesman, MD, PhD; Roland Faigle, MD, PhD

Background and Purpose—Intravenous thrombolysis (IVT) improves outcomes after acute ischemic stroke but is underused in certain patient populations. Mental illness is pervasive in the United States, and patients with comorbid psychiatric disease experience inequities in treatment for a range of conditions. We aimed to determine whether comorbid psychiatric disease is associated with differences in IVT use in acute ischemic stroke.

Methods—Acute ischemic stroke admissions between 2007 and 2011 were identified in the Nationwide Inpatient Sample. Psychiatric disease was defined by *International Classification of Diseases*, Ninth Revision, Clinical Modification codes for secondary diagnoses of schizophrenia or other psychoses, bipolar disorder, depression, or anxiety. Using logistic regression, we tested the association between IVT and psychiatric disease, controlling for demographic, clinical, and hospital factors.

Results—Of the 325 009 ischemic stroke cases meeting inclusion criteria, 12.8% had any of the specified psychiatric comorbidities. IVT was used in 3.6% of those with, and 4.4% of those without, psychiatric disease ($P<0.001$). Presence of any psychiatric disease was associated with lower odds of receiving IVT (adjusted odds ratio, 0.80; 95% confidence interval, 0.76–0.85). When psychiatric diagnoses were analyzed separately individuals with schizophrenia or other psychoses, anxiety, or depression each had significantly lower odds of IVT compared to individuals without psychiatric disease.

Conclusions—Acute ischemic stroke patients with comorbid psychiatric disease have significantly lower odds of IVT. Understanding barriers to IVT use in such patients may help in developing interventions to increase access to evidence-based stroke care. **(*Stroke*. 2018;49:738-740. DOI: 10.1161/STROKEAHA.117.020295.)**

Key Words: anxiety ■ depression ■ healthcare disparities ■ mental disorders ■ schizophrenia ■ stroke ■ thrombolytic therapy

Intravenous thrombolysis (IVT) with tPA (tissue-type plasminogen activator) is the cornerstone of acute ischemic stroke therapy.[1] However, IVT is underused in certain patient populations, including ethnic minorities, women, patients from low-income neighborhoods, and those covered by Medicare or Medicaid.[2–4]

An estimated 18% of adults in the United States have a mental illness within a given year.[5] Patients with comorbid psychiatric disease are vulnerable to inequities in treatment for a range of conditions,[6] and excess mortality in adults with severe mental illness is primarily attributable to nonpsychiatric diseases, including cardio- and cerebrovascular disease.[7] Stroke patients with comorbid psychiatric disease are significantly less likely to receive cerebrovascular arteriography and carotid endarterectomy and are more likely to be rehospitalized or die within 6 months of a stroke, compared with those without psychiatric disease.[8,9]

In the present study, we aimed to determine whether the presence of comorbid psychiatric disease is associated with lower IVT utilization in a representative sample of US adults presenting with ischemic stroke. Understanding barriers to IVT use in these patients may inform future interventions aimed at improving outcomes in stroke patients with psychiatric disease.

Methods

Data Source

Data were obtained from the Nationwide Inpatient Sample (NIS). The NIS is the largest all-payer inpatient database in the United States, representing all discharges from a 20% stratified sample of nonfederal US hospitals. NIS data are deidentified and are available per request to the Agency for Healthcare Research and Quality (http://www.hcup-us.ahrq.gov). This study was exempt from institutional review board approval.

Case Selection, Primary Exposure, and Outcome

We identified adult cases with a primary diagnosis of acute ischemic stroke between 2007 and 2011 by using *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM)

Received October 12, 2017; final revision received November 29, 2017; accepted December 21, 2017.

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Presented in part at the International Stroke Conference, Los Angeles, CA, January 26, 2018.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.020295/-/DC1.

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codes.[2] Patients admitted electively or enrolled in a clinical trial were excluded. Patients transferred in from another hospital were excluded to prevent duplicate records. Records missing information on age, sex, race/ethnicity, income, key hospital characteristics, or insurance status were also excluded. Finally, we excluded patients who received IVT later than day one of their hospital stay and those missing data for the day of IVT administration.

The primary exposure of interest was the presence of comorbid psychiatric disease, as identified by ICD-9-CM codes for secondary diagnoses of schizophrenia or other psychoses, bipolar disorder, depression, or anxiety (Table I in the online-only Data Supplement). The outcome of interest was IVT administration, as identified by ICD-9-CM code 99.10.

Comorbidity/Severity Adjustment

Comorbidities were measured using a modified Charlson comorbidity index.[4,10] Because substance abuse may be associated with laboratory abnormalities (such as coagulopathy and thrombocytopenia), refractory hypertension, and other potential contraindications to IVT, it was included as a covariate in our models rather than considered part of the primary exposure of interest. Substance abuse was defined using ICD-9-CM codes (Table II in the online-only Data Supplement). The All Patient Refined–Diagnosis-Related Groups were used to classify the patient's degree of loss of function as described previously.[2]

Statistical Analysis

Demographic, clinical, and hospital characteristics were compared between those with and without psychiatric disease using $\chi 2$ for categorical variables and Wilcoxon rank-sum tests for continuous variables. Logistic regression was used to test the association between IVT and presence of a psychiatric comorbidity. Multivariable models accounted for the stratified cluster design of the NIS and were adjusted for patient demographics (age, sex, race/ethnicity, primary expected payer, and median household income in patient's ZIP Code), hospital characteristics (region, location, teaching status, bed size, and annual stroke case volume), admission year, weekend admission, and clinical characteristics (modified Charlson comorbidity index, All Patient Refined–Diagnosis-Related Group, diabetes mellitus, coronary artery disease, hypertension, hypercholesterolemia, atrial fibrillation, valvular disease, peripheral vascular disorders, renal failure, obesity, coagulopathy, anemia, thrombocytopenia, and substance abuse). In addition, we analyzed the association between each psychiatric diagnosis and IVT use separately, controlling for the other psychiatric comorbidities. Potential interactions between psychiatric comorbidity and race/ethnicity, and between psychiatric comorbidity and sex, were explored. Statistical analyses were conducted using Stata version 14 (College Station, TX). Statistically significant results were defined as $P<0.05$, with 95% confidence intervals (CIs) reported.

Results

Sample Characteristics

Of the 325 009 cases that met inclusion criteria (Figure I in the online-only Data Supplement), 41 510 (12.8%) had any of the 4 psychiatric comorbidities of interest. The median age among patients with and without psychiatric comorbidities was 72 (interquartile range, 59–82) and 74 years (interquartile range, 62–83), respectively. Other demographic, clinical, and hospital characteristics of the study population are presented in Table III in the online-only Data Supplement.

Comorbid Psychiatric Disease Is Associated With Lower Odds of IVT

IVT was administered in 4.4% of stroke patients without psychiatric disease (95% CI, 4.2%–4.7%) and 3.6% of those with psychiatric disease (95% CI, 3.3%–3.9%; $P<0.001$). In univariate analysis, the presence of any of the 4 psychiatric comorbidities was associated with significantly lower odds of receiving IVT (Table). In the fully adjusted logistic regression model, the presence of any psychiatric comorbidity was associated with 20% lower odds of receiving IVT (odds ratio, 0.80; 95% CI, 0.76–0.85; Table; Figure). When evaluating the association between IVT use and individual psychiatric diagnoses, comorbid schizophrenia or other psychoses, depression, and anxiety were each independently associated with reduced odds of IVT (Table; Figure). The association between bipolar disorder and IVT did not reach statistical significance.

Table. Crude and Adjusted ORs of IVT Stratified by Psychiatric Disease Status in the Study Population (n=325 009)

Exposure	n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Any psychiatric disease	41 510 (12.8)	0.81 (0.77–0.86)	0.80 (0.76–0.85)
Schizophrenia/ psychosis	4368 (1.3)	0.56 (0.46–0.68)	0.61 (0.50–0.74)
Anxiety	12 375 (3.8)	0.87 (0.79–0.97)	0.88 (0.79–0.97)
Depression	25 394 (7.8)	0.84 (0.79–0.90)	0.85 (0.79–0.91)
Bipolar disorder	2841 (0.9)	0.93 (0.77–1.11)	0.86 (0.71–1.05)

CI indicates confidence interval; IVT, intravenous thrombolysis; and OR, odds ratio.

Interactions between psychiatric comorbidity and sex, and between psychiatric comorbidity and race/ethnicity, were explored. The adjusted odds of IVT in patients with, compared with without, psychiatric comorbidity was similar in women (odds ratio, 0.78; 95% CI, 0.72–0.84) compared with men (odds ratio, 0.84; 95% CI, 0.77–0.91; P interaction=0.151). Similarly, there was no significant interaction between psychiatric comorbidity and race (P interaction=0.873).

Discussion

In this study, acute stroke patients with comorbid psychiatric disease had significantly lower odds of receiving IVT. Moreover, when analyzed separately, schizophrenia or other psychoses,

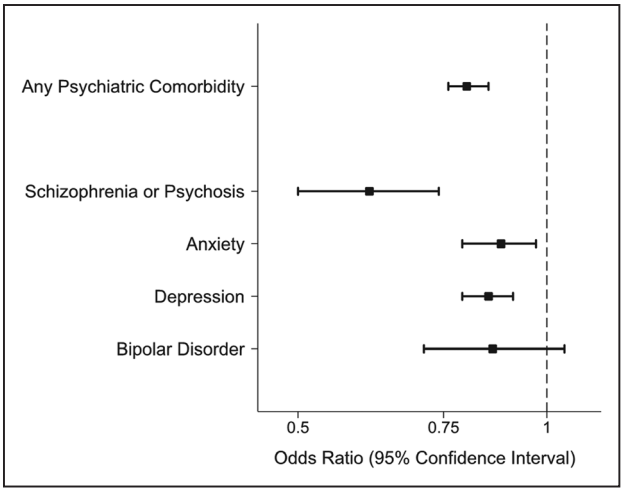

Figure. Multivariable logistic regression models for intravenous thrombolysis (IVT) use among stroke patients with psychiatric comorbidities.

anxiety, and depression were each associated with significantly lower odds of IVT. The effect size of the observed differences in IVT use associated with psychiatric disease is comparable to disparities in IVT use that have been demonstrated in other vulnerable stroke patients, such as racial minorities.[2] Patients with schizophrenia or psychoses were less likely to receive IVT than those with anxiety or depression. This finding is consistent with reports suggesting that schizophrenia is one of the leading contributors to disability globally and may be the psychiatric disease associated with the greatest impairment.[11]

Our analysis did not enable us to formally investigate reasons for the observed differences in IVT use; however, both patient and provider characteristics may explain the differences observed in our study. Psychiatric disease is associated with inadequate social support,[12] which may result in delayed hospital presentation, either because of delayed symptom recognition or delayed activation of Emergency Medical Services. Indeed, stroke patients who live alone are significantly less likely to arrive at the hospital in a timely manner, and less likely to receive IVT, compared with those who do not live alone.[13] Provider attitudes and implicit bias have been shown to influence medical decision-making[14] and may also contribute to lower rates of IVT in patients with mental illness. Moreover, determining eligibility for IVT relies on patient history, and providers might consider stroke patients with psychiatric disease unreliable historians. Faced with diagnostic uncertainty, physicians might be more likely to ascribe stroke symptoms to a preexisting psychiatric disease[15] or a conversion disorder, which may delay stroke diagnosis and preclude consideration of IVT.

Limitations of the study include use of an administrative data set that relies on ICD-9-CM coding and inpatient discharge records. Identification of psychiatric disease using only inpatient diagnosis codes may have missed some patients with psychiatric diagnoses. Furthermore, in our analysis, the presence of a psychiatric comorbidity did not distinguish between active versus remote history of psychiatric disease, and information on disease severity was not available. In addition, NIS does not include information on clinical stroke characteristics, medications, or contraindications to IVT, such as delay in presentation. Lastly, data on provider attitudes and implicit biases were not available. Despite these limitations, our study suggests that acute ischemic stroke patients with psychiatric disease are less likely to receive IVT. Future studies may address the underlying mechanisms of such treatment differences to develop interventions aimed at facilitating equal stroke care for all.

Sources of Funding

D.M. Bongiorno is supported by The Johns Hopkins School of Medicine William Walker Award for Psychiatric Research. Drs Daumit, Gottesman, and Faigle are supported by the following National Institutes of Health grants: National Institute of Mental Health (NIMH) K24MH093763 (Dr Daumit); National Institute on Aging (NIA) K24AG052573 (Dr Gottesman), and National Institute of Neurological Disorders and Stroke (NINDS) K23NS101124 (Dr Faigle).

Disclosures

Dr Gottesman is an Associate Editor for Neurology. The other authors report no conflicts.

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Stroke
Journal of the American Heart Association

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Stroke. 2018;49:738-740; originally published online January 26, 2018;
doi: 10.1161/STROKEAHA.117.020295
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Supplemental Table I. ICD9-CM codes used to identify those with comorbid psychiatric disease.

Subgroup	ICD9-CM code	Code description
Schizophrenia or other psychoses	295.00-295.05	Simple type schizophrenia
	295.10-295.15	Disorganized type schizophrenia
	295.20-295.25	Catatonic type schizophrenia
	295.30-295.35	Paranoid type schizophrenia
	295.40-295.45	Schizophreniform disorder
	295.50-295.55	Latent schizophrenia
	295.60-295.65	Schizophrenic disorders, residual type
	295.70-295.75	Schizoaffective disorder
	295.80-295.85	Other specified types of schizophrenia
	295.90-295.95	Unspecified schizophrenia
	297.0	Paranoid state, simple
	297.8	Other specified paranoid states
	297.9	Unspecified paranoid state
	298.0	Depressive type psychosis
	298.1	Excitative type psychosis
	298.4	Psychogenic paranoid psychosis
	298.8	Other and unspecified reactive psychosis
	298.9	Unspecified psychosis
Depression	296.20-296.26	Major depressive affective disorder, single episode
	296.30-296.36	Major depressive affective disorder, recurrent episode
	296.90	Unspecified episodic mood disorder
	311	Depressive disorder, not elsewhere classified
Bipolar disorder	296.00-296.06	Bipolar I disorder, single manic episode
	296.40-296.46	Bipolar I disorder, most recent episode (or current) manic
	296.50-296.56	Bipolar I disorder, most recent episode (or current) depressed
	296.60-296.66	Bipolar I disorder, most recent episode (or current) mixed
	296.7	Bipolar I disorder, most recent episode (or current) unspecified
	296.80	Bipolar disorder, unspecified
	296.81	Atypical manic disorder
	296.82	Atypical depressive disorder
	296.89	Other bipolar disorders
Anxiety	293.84	Anxiety disorder in conditions classified elsewhere
	300.00	Anxiety state, unspecified
	300.01	Panic disorder without agoraphobia
	300.02	Generalized anxiety disorder
	300.09	Other anxiety states
	300.21	Agoraphobia with panic disorder
	300.22	Agoraphobia without mention of panic attacks
	300.23	Social phobia
	300.3	Obsessive-compulsive disorders
	300.7	Hypochondriasis
	309.81	Posttraumatic stress disorder

Supplemental Table II. ICD9-CM codes used to define current substance abuse and dependence.

Subgroup	ICD9-CM code	Code description
Alcohol dependence	303.00	Acute alcoholic intoxication in alcoholism, unspecified
	303.01	Acute alcoholic intoxication in alcoholism, continuous
	303.02	Acute alcoholic intoxication in alcoholism, episodic
	303.90	Other and unspecified alcohol dependence, unspecified
	303.91	Other and unspecified alcohol dependence, continuous
	303.92	Other and unspecified alcohol dependence, episodic
Non-alcohol depressant dependence	304.00	Opioid type dependence, unspecified
	304.01	Opioid type dependence, continuous
	304.02	Opioid type dependence, episodic
	304.10	Sedative, hypnotic or anxiolytic dependence, unspecified
	304.11	Sedative, hypnotic or anxiolytic dependence, continuous
	304.12	Sedative, hypnotic or anxiolytic dependence, episodic
Stimulant dependence	304.20	Cocaine dependence, unspecified
	304.21	Cocaine dependence, continuous
	304.22	Cocaine dependence, episodic
	304.40	Amphetamine and other psychostimulant dependence, unspecified
	304.41	Amphetamine and other psychostimulant dependence, continuous
	304.42	Amphetamine and other psychostimulant dependence, episodic
Cannabis dependence	304.30	Cannabis dependence, unspecified
	304.31	Cannabis dependence, continuous
	304.32	Cannabis dependence, episodic
Alcohol abuse	305.00	Alcohol abuse, unspecified
	305.01	Alcohol abuse, continuous
	305.02	Alcohol abuse, episodic
Cannabis abuse	305.20	Cannabis abuse, unspecified
	305.21	Cannabis abuse, continuous
	305.22	Cannabis abuse, episodic
Non-alcohol depressant abuse	305.40	Sedative, hypnotic or anxiolytic abuse, unspecified
	305.41	Sedative, hypnotic or anxiolytic abuse, continuous
	305.42	Sedative, hypnotic or anxiolytic abuse, episodic
	305.50	Opioid abuse, unspecified
	305.51	Opioid abuse, continuous
	305.52	Opioid abuse, episodic
Stimulant abuse	305.60	Cocaine abuse, unspecified
	305.61	Cocaine abuse, continuous
	305.62	Cocaine abuse, episodic
	305.70	Amphetamine or related acting sympathomimetic abuse, unspecified
	305.71	Amphetamine or related acting sympathomimetic abuse, continuous
	305.72	Amphetamine or related acting sympathomimetic abuse, episodic

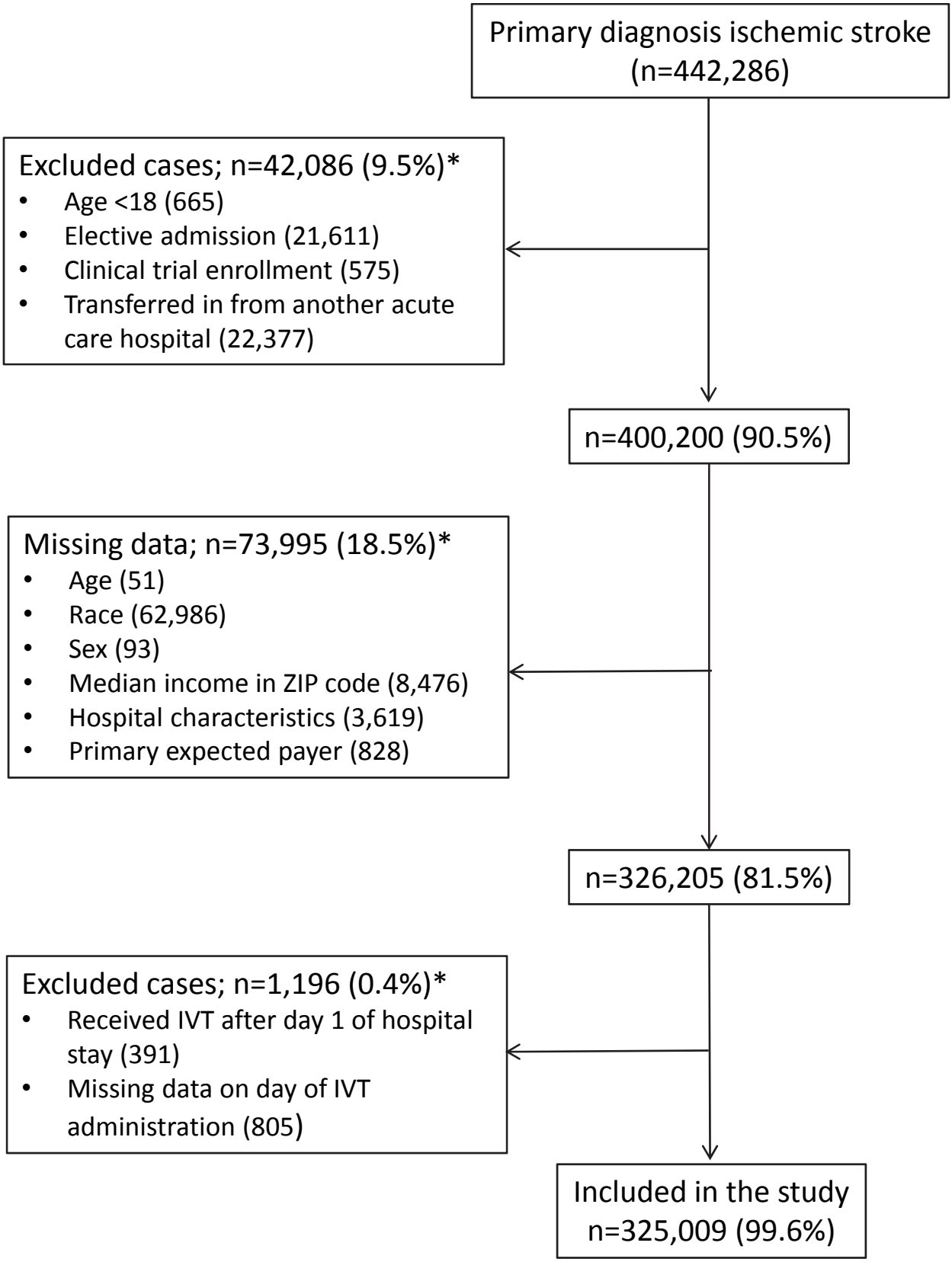
Supplemental Table III. Baseline characteristics of the study population stratified by presence of any comorbid psychiatric disease (n=325,009). CCI: Charlson comorbidity index. APR-DRG: all patient refined diagnosis-related group.

Characteristics	No psychiatric comorbidity (n=283,499)	Psychiatric comorbidity (n=41,510)	p-value
Age – years: median (IQR)	74 (62-83)	72 (59-82)	<0.001
Female – n (%)	147,378 (52.0)	26,340 (63.5)	<0.001
Race/ethnicity – n (%)			<0.001
White	195,521 (69.0)	32,089 (77.3)	
Black	49,752 (17.6)	5,144 (12.4)	
Hispanic	21,380 (7.5)	2,644 (6.4)	
Asian or Pacific Islander	8,273 (2.9)	585 (1.4)	
Other	8,573 (3.0)	1,048 (2.5)	
Primary expected payer – n (%)			<0.001
Private Insurance	55,343 (19.5)	7,413 (17.9)	
Medicare	188,529 (66.5)	28,046 (67.6)	
Medicaid	18,011 (6.4)	3,498 (8.4)	
Self-pay	14,060 (5.0)	1,472 (3.6)	
No charge/other	7,556 (2.7)	1,081 (2.6)	
Median household income in patient ZIP code – n (%)			<0.001
Quartile 1	82,126 (29.0)	11,669 (28.1)	
Quartile 2	71,428 (25.2)	10,505 (25.3)	
Quartile 3	66,809 (23.6)	10,234 (24.7)	
Quartile 4	63,136 (22.3)	9,102 (21.9)	
Weekend admission	73,941 (26.1)	10,431 (25.1)	<0.001
Hospital region – n (%)			<0.001
Northeast	60,498 (21.3)	7,994 (19.3)	
Midwest	43,100 (15.2)	7,738 (18.6)	
South	121,916 (43.0)	17,106 (41.2)	
West	57,985 (20.5)	8,672 (20.9)	
Hospital location – n (%)			<0.001
Rural	33,769 (11.9)	5,236 (12.6)	
Urban	249,730 (88.1)	36,274 (87.4)	
Teaching Hospital – n (%)	121,906 (43.0)	17,373 (41.9)	<0.001
Hospital bed size – n (%)			<0.001
Small	32,595 (11.5)	5,125 (12.4)	
Medium	69,712 (24.6)	10,237 (24.7)	
Large	181,192 (63.9)	26,148 (63.0)	

Hospital annual stroke case volume			<0.001
Quartile 1	71,224 (25.1)	10,992 (26.5)	
Quartile 2	71,131 (25.1)	9,943 (24.0)	
Quartile 3	70,110 (24.7)	10,637 (25.6)	
Quartile 4	71,034 (25.1)	9,938 (23.9)	
Modified CCI – n (%)			<0.001
0	103,250 (36.4)	13,961 (33.6)	
1	97,185 (34.3)	14,164 (34.1)	
2	49,866 (17.6)	7,794 (18.8)	
3	19,612 (6.9)	3,350 (8.1)	
4	6,494 (2.3)	1,141 (2.8)	
>4	7,092 (2.5)	1,100 (2.7)	
Diabetes Mellitus – n (%)	96,315 (34.0)	13,890 (33.5)	0.040
Coronary artery disease – n (%)	67,759 (23.9)	9,836 (23.7)	0.359
Hypertension – n (%)	227,063 (80.1)	33,594 (80.9)	<0.001
Hypercholesterolemia – n (%)	134,516 (47.5)	21,287 (51.3)	<0.001
Atrial fibrillation – n (%)	65,311 (23.0)	7,907 (19.1)	<0.001
Valvular disease – n (%)	29,342 (10.4)	4,053 (9.8)	<0.001
Peripheral vascular disease – n (%)	25,213 (8.9)	3,881 (9.4)	0.002
Renal failure – n (%)	36,430 (12.9)	4,946 (11.9)	<0.001
Obesity – n (%)	21,012 (7.4)	4,049 (9.8)	<0.001
Coagulopathy	7,525 (2.7)	1,025 (2.5)	0.028
Anemia	35,584 (12.6)	5,934 (14.3)	<0.001
Thrombocytopenia – n (%)	5,841 (2.1)	797 (1.9)	0.059
Substance abuse – n (%)	12,267 (4.3)	2,233 (5.4)	<0.001
APR-DRG: Loss of function			<0.001
Minor	27,511 (9.7)	3,390 (8.2)	
Moderate	137,814 (48.6)	20,683 (49.8)	
Major	93,476 (33.0)	14,497 (34.9)	
Extreme	24,698 (8.7)	2,940 (7.1)	
Died – n (%)	14,147 (5.0)	1,333 (3.2)	<0.001
Missing	182 (0.1)	32 (0.1)	

Supplemental Figure Legend

Supplemental Figure I. Flow diagram indicating case selection. *Categories are not mutually exclusive.



Supplemental Figure I