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Comparison of Short-term Outcomes of Thrombolysis for In-hospital Stroke and Out-of-hospital Stroke in US

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Abstract

Background and Purpose—In-hospital stroke (IHS) differs from out-of-hospital stroke (OHS) in risk factors and outcomes. We compared IHS and OHS treated with thrombolysis from a large national cohort in a cross-sectional study to further clarify these differences.

Methods—The Nationwide Inpatient Sample for the years 2005 through 2010 was searched for adult acute ischemic stroke cases treated with intravenous or intra-arterial thrombolysis. Patients treated on the day of admission were classified as OHS. We compared the demographic and hospital characteristics, comorbidities, and short-term outcomes of thrombolysed IHS and OHS.

Results—IHS represented 8.7% of 11,750 thrombolysed stroke cases included in this study. IHS was associated with a higher comorbidity profile and higher rates of acute medical conditions compared to OHS. IHS had higher inpatient mortality (15.7% versus 9.6%; P<0.001) and lower rate of discharge to home/self-care (22.8% versus 30.0%; P<0.001). IHS was also associated with higher mortality among endovascular treatment group (19.3% versus 13.8%; P=0.010). The difference in the rate of all intracerebral hemorrhage (ICH) was not significant (5.3% versus 4.7%; P=0.361). In the multivariate analysis, inpatient mortality (adjusted OR, 1.59; 95% CI, 1.32–1.92; P<0.001) and favorable discharge outcome (adjusted OR, 0.79; 95% CI, 0.67–0.93; P=0.005) remained significantly worse in IHS.

Conclusions—Thrombolysed IHS is associated with worse discharge outcomes compared to thrombolysed OHS, likely due to their higher comorbidities and additional medical reasons for the index admission. Thrombolysis is not associated with a higher rate of ICH among IHS.

Keywords

in-hospital stroke; thrombolysis; ischemic stroke; intracerebral hemorrhage; nationwide inpatient sample

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Introduction

Hospitalized patients are at a higher risk of stroke than the general population.[1] An estimated 35,000–75,000 cases of stroke occur in patients admitted to the hospital for another reason [in-hospital stroke (IHS)] each year in the United States representing 4%–17% of all stroke cases.[2] Factors contributing to the incidence of IHS include withdrawal of antiplatelet/anticoagulant agents, active cancer, cardiac diseases, cardiovascular surgeries/minimally invasive procedures, hypotension and infections.[3–5] IHS differs from the stroke with onset outside of the hospital [out-of-hospital stroke (OHS)] in mechanism, severity and outcomes. IHS is more likely to be cardioembolic and have multiple territorial infarctions than OHS while small vessel occlusions are rare in IHS.[6–9] Furthermore, IHS is associated with higher inpatient mortality and worse functional outcomes.[6, 8, 10, 11]

IHS cases are excellent candidates for time-sensitive thrombolytic treatment as they avoid the pre-hospital delays. However, decision to give thrombolytic treatment in IHS may be complicated by comorbidities, acute medical illness responsible for index hospitalization, and other medical and surgical contraindications for thrombolysis. Masjuan et al[12] studied IHS and OHS treated with thrombolysis in a multi-center study and found a paradoxical trend toward higher inpatient mortality among OHSs, partly due to small sample size leading to inconclusive results. Large-scale studies comparing thrombolysis in IHS and OHS are lacking. Therefore, we sought to compare the comorbidities, medical complications, and outcomes of IHS and OHS treated with intravenous (IV) or intra-arterial thrombolysis from a national database.

Methods

Data-source

The Nationwide Inpatient Sample (NIS) for years 2005 through 2010 was obtained from the Agency for Healthcare Research and Quality (AHRQ) for analysis. NIS, the largest all-payer inpatient database in the US, is a 20% stratified sample of all hospitalizations in non-federal hospitals. Approximately 1,000 hospitals are sampled each year and all the inpatient admissions from the sampled hospitals are included in NIS. It contains more than100 clinical and non-clinical discharge level variables including primary and secondary diagnoses, in-hospital procedures including the day of the procedure from the admission, demographic and hospital characteristics, and discharge outcomes. Detailed information regarding the content and the methodology of NIS is available at the AHRQ website http://www.hcup-us.ahrq.gov/nisoverview.jsp (accessed December 1, 2012).[13]

Case selection

Figure 1 shows case selection flowchart of the study. Ascertainment of all diagnoses and procedures was made by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes recorded at discharge (Supplemental Table S1; http://stroke.ahajournals.org). Acute ischemic stroke cases of age >18 years were selected using ICD-9 codes 433.×1, 434.×1, or 436,[13–16] and thrombolytic infusion was ascertained by procedure code 99.10.[17, 18] As NIS database lacks explicit IHS variable, cases were classified as OHS if thrombolytic treatment was administered on the day of hospitalization and as IHS if thrombolytic treatment was given on the second day of hospitalization or later. Cases with missing information regarding the thrombolysis day were excluded from the study. Patients transferred from another hospital were also excluded as they may have developed symptoms while in the previous hospital but received thrombolysis on the day of arrival to the current hospital. Additionally, the cases with acute myocardial infarction or

pulmonary embolism and those on dialysis (with possibly clotted access) were excluded to avoid uncertainty of indication for thrombolytic infusion.

The Elixhauser comorbidities,[19] modified to create a weighted numeric score as recommended by van Walraven et al,[20] were used to quantify patients' comorbidity profiles. The Elixhauser comorbidities have been validated for prognostication in studies using administrative datasets with ICD-9 codes.[21–23] The primary outcomes of the study were favorable discharge disposition defined as discharge to home/self-care and inpatient mortality. Secondary outcomes were symptomatic or asymptomatic intracerebral hemorrhage (ICH), gastrointestinal (GI) bleeding, tracheostomy and gastrostomy tube placement. Endovascular treatment was ascertained by the performance of invasive cerebral angiogram (ICD-9 procedure code 88.41) with thrombolytic infusion (99.10), and/or mechanical thrombectomy (39.74).[24, 25] We compared the outcomes of IHS and OHS among IV thrombolysis only and endovascular thrombolysis groups.

Statistical analysis

Non-parametric Elixhauser index was categorized into the following quartiles: (1) <5, (2) 5–7, (3) 8–14, and (4) >14. Missing ethnicity data (14.5%) were coded as 'missing information' without any imputation. Comparisons were made by Pearson χ^2 for categorical variables. Mantel–Haenszel test was used to calculate unadjusted odds ratios. Outcomes were adjusted using multivariate logistic regression after controlling for age-group, gender, ethnicity, hospital characteristics such as bed-size, location/teaching status and region and Elixhauser index. Hosmer-Lemeshow test was used to assess goodness-of-fit of the regression models. All analyses were performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, Illinois) with statistical significance set at 0.05.

Results

Of the 11,750 thrombolysed ischemic strokes included in the study, 1,020 (8.7%) were IHSs. Age and gender distributions between IHS and OHS cohorts were not significantly different. IHS was more common in large sized and urban teaching hospitals and hospitals in the northeast region of the US (Table 1). Comparison of baseline characteristics and outcomes of cases with missing thrombolysis day (13.7%) to those with known thrombolysis day is shown in Supplemental Table S2. The cases with missing thrombolysis day were more likely to be from midwest and large-sized urban teaching hospitals.

On univariate analysis, IHS had significantly higher Elixhauser comorbidity index compared to OHS. Dyslipidemia and hypertension were more common in OHS. IHSs were more likely to have atrial fibrillation, coronary artery disease, chronic kidney disease, congestive heart failure, coagulopathy, diabetes with chronic complications, metastatic cancer and solid tumor without metastasis. In-hospital acute medical conditions associated with IHS were acute kidney injury, acute respiratory failure, cardiac arrest, deep venous thrombosis, pneumonia, sepsis and urinary infection (Table 2).

IHS had higher unadjusted inpatient mortality (15.7% versus 9.6%; odds ratio [OR], 1.76; 95% confidence interval [CI], 1.47–2.11, P<0.001) and lower favorable discharge disposition rate (22.8% versus 30.0%; OR, 0.69; 95% CI, 0.59–0.81, P<0.001) compared to OHS. The unadjusted rate of all ICH did not differ significantly between the two groups (5.3% versus 4.7%; OR, 1.14; 95% CI, 0.86–1.53; P=0.361) (Figure 2). Univariate outcomes by endovascular treatment showed higher inpatient mortality and lower rate of favorable discharge among IHS treated with IV thrombolysis only as well as among IHS treated with endovascular treatment (Table 3). In the multivariate analysis, IHS was associated with

lower rate of discharge to home/self-care (adjusted OR, 0.79; 95% CI, 0.67–0.93; P=0.005) and higher inpatient mortality (adjusted OR, 1.59; 95% CI, 1.32–1.92; P<0.001) (Table 4).

Discussion

Our data suggest that inpatient mortality is higher and favorable discharge disposition is lower in thrombolysed IHS compared to thrombolysed OHS. Previous studies have shown that IHSs are more likely to be embolic resulting in more severe deficits at onset.[3, 7, 25, 26] Kimura et al[8] reported higher median National Institutes of Health Stroke Scale (NIHSS) in IHS compared to OHS. These studies indicate that IHS represents more severe stroke cases with poorer expected outcomes with or without thrombolytic treatment. Additionally, evaluation of the IHS patients may be delayed for various reasons such as the use of sedative or paralytic medications, delirium, and complexities of hospital practice leading to longer in-hospital delays among IHS, further contributing to the poor outcomes.[11, 12]

While we did not find difference in age distribution between the two groups, Kimura et al[8] found that IHS patients were older than OHS. As our study included only the patients treated with thrombolysis, this finding might suggest that elderly IHS patients were preferentially excluded from thrombolytic treatment by the treating clinicians. We could not find previous reports comparing hospital characteristics between IHS and OHS. We found that the rate of thrombolysed IHS was higher in large sized, urban teaching hospitals, a finding potentially indicative of greater adherence of academic institutions to evidence based use of thrombolytic treatment irrespective of the in-hospital onset of the stroke. Vera et al[11] found higher comorbidities in patients with IHS. Similarly, in this study, IHS had significantly higher Elixhauser comorbidity index which is associated with worse outcomes after stroke.[23] Similar to prior reports,[6, 8, 9, 12] IHS had higher rate of atrial fibrillation and lower rates of dyslipidemia and hypertension in our study. Of note, several comparisons in this study may have reached statistical significance with small absolute differences due to large sample size.

Despite the presumed higher use of antiplatelet and/or antithrombotic treatment[12] and higher incidence of embolic stroke with more severe deficits and larger infarct size among IHS, the rate of the most feared complication of thrombolysis (i.e., ICH) was not significantly different between the two groups, potentially implying relative safety of thrombolysis in IHS. The rate of all ICH in this study was lower than that in previous studies reporting symptomatic ICH[27, 28] likely due to under-ascertainment of hemorrhagic conversion of ischemic stroke using the only available ICD-9 code for intracerebral hemorrhage.

Higher use of endovascular treatment in IHS may be suggestive of more number of patients not eligible for systemic thrombolysis due to recent surgery or bleeding, or higher clot burden and therefore greater resistance to recanalization by IV thrombolysis alone in IHS.[29] The worse outcomes in the endovascular group may be due to selective endovascular treatment of patients with more severe deficits, delayed recognition of stroke, or poor response to systemic thrombolysis.

This study has several important limitations related to the administrative nature of the database. NIS database lacks information regarding symptom onset. Therefore, we used the day of thrombolysis in relation to the day of admission to define IHS indirectly. Though this definition is expected to correctly identify a vast majority of IHS cases, misclassification is possible. For instance, IHS patients that developed the symptoms on the day of hospitalization and subsequently were given treatment on the same day are incorrectly classified as OHS. Similarly, OHS cases admitted before midnight and treated after midnight would be misclassified as IHS. NIS also lacks stroke severity measure such as

NIHSS, a strong predictor of the outcome,[30] thus limiting the adjusted analyses. NIS does not contain standard outcome measure such as 3-month modified Rankin Scale (mRS) or etiologic classification such as Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype. However, discharge destination as a surrogate for functional status has been shown to have high predictive value for 3- and 12-month post-stroke mRS.[31] Coding error is another potential source of bias. However, the ICD-9 codes used to select acute ischemic stroke have high specificity and positive predictive value.[14–16, 32] The ICD-9 procedure code 99.10 has the sensitivity of 55–70% and the specificity of 98% for thrombolytic treatment in stroke.[33–35] Therefore, under-ascertainment is possible but case identification is likely to be accurate. We were not able to differentiate symptomatic from asymptomatic ICH due to lack of clinical data in NIS. Finally, the differences in the geographic distribution and hospital characteristics of included and excluded cases might potentially have introduced bias. Despite the limitations, inclusion of large number of patients from various demographic backgrounds and from academic and non-academic institutions makes the results highly generalizable.

Conclusions

In conclusion, IHS comprises of a significant subgroup of stroke with greater potential for thrombolytic treatment benefit as they avoid pre-hospital delays. However, IHS results in worse short-term outcomes when compared to OHS due to their coexistent medical illnesses and comorbidities. Despite IHS being a high risk group for complications of thrombolytic treatment, the rate of ICH in IHS was comparable to that in OHS in our study, potentially indicating relative safety of thrombolysis in IHS. Prospective studies of thrombolytic therapy for IHS from clinical data-source are needed to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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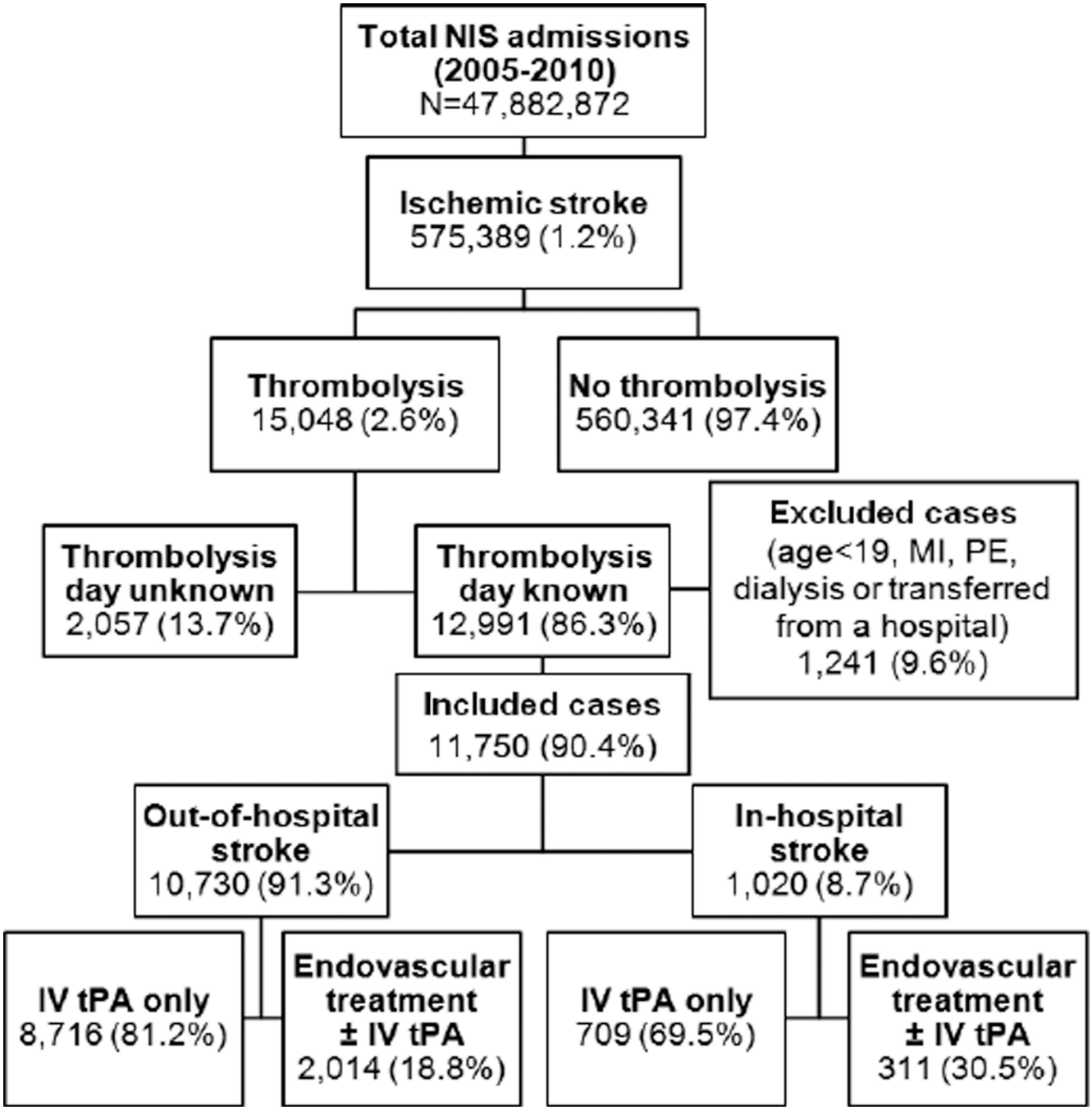

Figure 1.
Case-selection Flowchart. Endovascular treatment includes intra-arterial thrombolysis and/or mechanical embolectomy. IV indicates intravenous; MI, myocardial infarction; NIS, nationwide inpatient sample; PE, pulmonary embolism; tPA, tissue plasminogen activator.

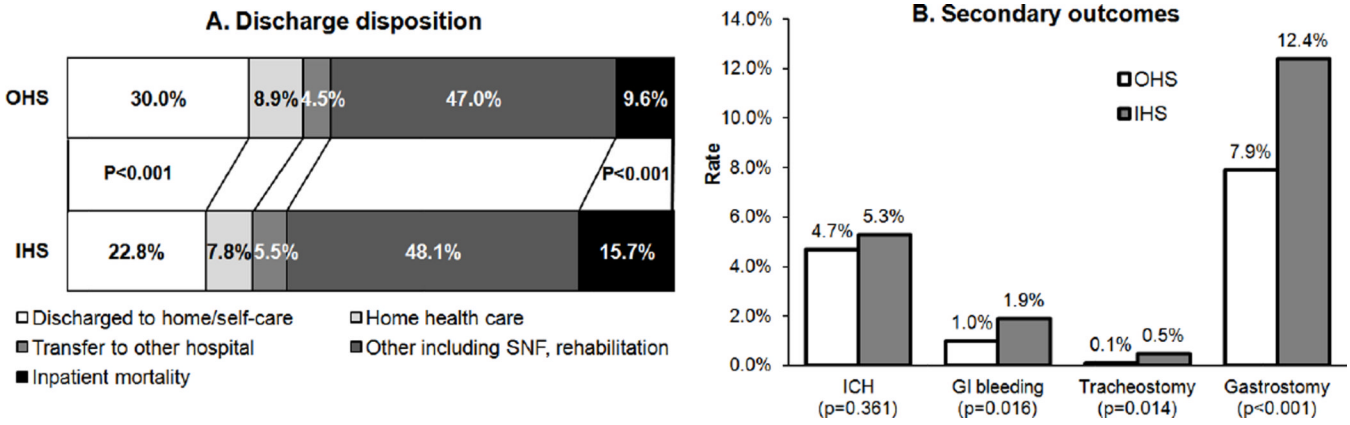

Figure 2.

Comparison of Outcomes between Thrombolysed In-Hospital Stroke and Out-of-Hospital Stroke. GI indicates gastrointestinal; ICH, intracerebral hemorrhage; IHS, in-hospital stroke; OHS, out-of-hospital stroke; and SNF, skilled nursing facility.

Table 1

Descriptive Summary of Baseline Demographic and Hospital Characteristics of Thrombolysed In-Hospital and Out-of-Hospital Strokes in the United States, 2005–2010.

	OHS, n (%)	IHS, n (%)	P value
No. of cases	10,730 (91.3)	1,020 (8.7)	--
Age-group, y			0.726
19–64	4029 (37.5)	371 (36.4)	
65–79	3738 (34.8)	366 (35.9)	
80 or more	2963 (27.6)	283 (27.7)	
Female gender	5238 (48.8)	529 (51.9)	0.063
Ethnicity			0.032
Caucasian	6889 (64.2)	684 (67.1)	
African-American	1366 (12.7)	120 (11.8)	
Hispanic	632 (5.9)	65 (6.4)	
Other	523 (4.9)	57 (5.6)	
Missing information	1320 (12.3)	94 (9.2)	
Primary payer			0.017
Medicare	6248 (58.2)	603 (59.1)	
Medicaid	709 (6.6)	85 (8.3)	
Private insurance	2940 (27.4)	242 (23.7)	
Other	833 (7.8)	90 (8.8)	
Location/teaching status			<0.001
Rural	602 (5.7)	45 (4.5)	
Urban, nonteaching	4311 (40.7)	347 (34.4)	
Urban, teaching	5675 (53.6)	616 (61.1)	
Hospital bed-size			0.002
Small	629 (5.9)	54 (5.4)	
Medium	2484 (23.5)	191 (18.9)	
Large	7475 (70.6)	763 (75.7)	
Geographic region			0.002
Northeast	2435 (22.7)	280 (27.5)	
Midwest	1722 (16.0)	140 (13.7)	
South	4306 (40.1)	378 (37.1)	
West	2267 (21.1)	222 (21.8)	

IHS indicates in-hospital stroke; OHS, out-of-hospital stroke.

Table 2

Univariate Comparison of Comorbidities and Acute Medical Conditions Associated with In-Hospital Stroke and Out-of-Hospital Stroke (United States Nationwide Inpatient Sample, 2005–2010)

	OHS, n (%)	IHS, n (%)	P value
Comorbidities			
Elixhauser comorbidity quartile (index value)			<0.001
1st (<5)	3013 (28.1)	212 (20.8)	
2nd (5–7)	2951 (27.5)	223 (21.9)	
3rd (8–14)	2824 (26.3)	292 (28.6)	
4th (>14)	1942 (18.1)	293 (28.7)	
Anemia	1116 (10.4)	203 (19.9)	<0.001
Atrial fibrillation	2531 (23.6)	269 (26.4)	0.046
Coronary artery disease	2810 (26.2)	330 (32.4)	<0.001
Chronic kidney disease	757 (7.1)	93 (9.1)	0.015
Coagulopathy	254 (2.4)	54 (5.3)	<0.001
Collagen vascular disease	219 (2.0)	14 (1.4)	0.143
Congestive heart failure	1352 (12.6)	156 (15.3)	0.014
Diabetes without complications	2456 (22.9)	240 (23.5)	0.642
Diabetes with chronic complications	298 (2.8)	47 (4.6)	0.001
Dyslipidemia	5112 (47.6)	408 (40.0)	<0.001
Hypertension	8133 (75.8)	721 (70.7)	<0.001
Liver disease	76 (0.7)	11 (1.1)	0.188
Metastatic cancer	75 (0.7)	17 (1.7)	0.001
Solid tumor without metastasis	132 (1.2)	23 (2.3)	0.006
Valvular disease	978 (9.1)	86 (8.4)	0.467
Medical complications			
Acute kidney injury	551 (5.1)	109 (10.7)	<0.001
Acute respiratory failure	959 (8.0)	176 (17.3)	<0.001
Cardiac arrest	56 (0.5)	20 (2.0)	<0.001
Deep venous thrombosis	82 (0.8)	24 (2.4)	<0.001
Pneumonia	434 (4.0)	112 (11.0)	<0.001
Sepsis	202 (1.9)	77 (7.5)	<0.001
Urinary infection	1213 (11.3)	196 (19.2)	<0.001

IHS indicates in-hospital stroke; OHS, out-of-hospital stroke.

Table 3

Univariate Comparison of Primary and Secondary Outcomes between In-Hospital Stroke and Out-of-Hospital Stroke by Endovascular Treatment Group

	IV thrombolysis only			Endovascular treatment ± IV thrombolysis		
	OHS	**IHS**	**P value**	**OHS**	**IHS**	**P value**
Inpatient mortality	8.6%	14.1%	<0.001	13.8%	19.3%	0.010
Discharge to home/self-care	30.9%	25.1%	0.001	26.0%	17.7%	0.002
All ICH	4.3%	5.2%	0.238	6.3%	5.5%	0.568
GI bleeding	1.1%	1.7%	0.136	0.8%	2.3%	0.022
Tracheostomy	0.1%	0.7%	<0.001	0.2%	0.0%	0.379
Gastrostomy	7.6%	12.4%	<0.001	8.8%	12.2%	0.056

GI indicates gastrointestinal; ICH, intracerebral hemorrhage; IHS, in-hospital stroke; and OHS, out-of-hospital stroke.

Table 4

Multivariate Analysis: In-Hospital Stroke as a Predictor of Discharge to Home/Self-care and Inpatient Mortality in Ischemic Strokes Treated with Thrombolysis.

	Discharge to home/self-care		Inpatient mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
IHS versus OHS	0.79 (0.67–0.93)	0.005	1.59 (1.32–1.92)	<0.001
Age, y (19–64)	Reference		Reference	
65–79	0.57 (0.51–0.62)	<0.001	1.49 (1.27–1.76)	<0.001
≥80	0.23 (0.20–0.27)	<0.001	2.16 (1.83–2.56)	<0.001
Female versus male	0.89 (0.81–0.97)	0.009	0.91 (0.80–1.03)	0.121
Ethnicity (Caucasian)	Reference		Reference	
African-American	0.94 (0.82–1.08)	0.365	0.89 (0.72–1.10)	0.290
Hispanic	0.91 (0.76–1.10)	0.334	0.99 (0.75–1.29)	0.929
Other	1.06 (0.87–1.30)	0.563	1.12 (0.85–1.48)	0.417
Missing information	0.99 (0.86–1.13)	0.870	1.15 (0.95–1.40)	0.149
Bed-size (small)	Reference		Reference	
Medium	1.11 (0.90–1.36)	0.334	1.18 (0.86–1.61)	0.305
Large	1.14 (0.94–1.39)	0.168	1.48 (1.10–1.98)	0.009
Location/teaching status (rural)	Reference		Reference	
Urban, non-teaching	0.89 (0.74–1.08)	0.256	1.09 (0.80–1.47)	0.586
Urban, teaching	0.98 (0.81–1.19)	0.827	1.38 (1.02–1.85)	0.036
Region (Northeast)	Reference		Reference	
Midwest	1.56 (1.34–1.80)	<0.001	0.71 (0.57–0.88)	0.002
South	1.46 (1.30–1.65)	<0.001	0.91 (0.78–1.07)	0.263
West	1.39 (1.21–1.60)	<0.001	0.95 (0.79–1.14)	0.554
Elixhauser index quartile (1st)	Reference		Reference	
2nd	0.44 (0.39–0.49)	<0.001	1.48 (1.22–1.81)	<0.001
3rd	0.33 (0.29–0.36)	<0.001	1.93 (1.60–2.34)	<0.001
4th	0.18 (0.15–0.21)	<0.001	2.63 (2.17–3.20)	<0.001

IHS indicates in-hospital stroke; and OHS, out-of-hospital stroke.