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BRIEF RESEARCH REPORT

Neurology

Delay in hospital presentation is the main reason large vessel occlusion stroke patients do not receive intravenous thrombolysi

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Abstract

Objectives: Intravenous thrombolysis (IVT) and endovascular therapy (EVT) are the mainstays of treatment for large vessel occlusion stroke (LVOS). Prior studies have examined why patients have not received IVT, the most cited reasons being last-known-well (LKW) to hospital arrival of >4.5 hours and minor/resolving stroke symptoms. Given that LVOS patients typically present moderate-to-severe neurologic deficits, these patients should be easier to identify and treat than patients with minor strokes. This investigation explores why IVT was not administered to a cohort of LVOS patients who underwent EVT.

Methods: This is an analysis of the Optimizing the Use of Prehospital Stroke Systems of Care (OPUS-REACH) registry, which contains patients from 9 endovascular centers who underwent EVT between 2015 and 2020. The exposure of interest was the receipt of intravenous thrombolysis. Descriptive summary statistics are presented as means and SDs for continuous variables and as frequencies with percentages for categorical

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variables. Two-sample *t* tests were used to compare continuous variables and the chi-square test was used to compare categorical variables between those who received IVT and those who did not receive EVT.

Results: Two thousand forty-three patients were included and 60% did not receive IVT. The most common reason for withholding IVT was LKW to arrival of >4.5 (57.2%). The second most common contraindication was oral anticoagulation (15.5%). On multivariable analysis, 2 factors were associated with not receiving IVT: increasing age (odds ratio [OR] 0.86; 95% confidence interval [CI] 0.78–0.93) and increasing time from LKW-to hospital arrival (OR 0.45 95% CI 0.46–0.49).

Conclusion: Like prior studies, the most frequent reason for exclusion from IVT was a LKW to hospital presentation of >4.5 hours; the second reason was anticoagulation. Efforts must be made to increase awareness of the time-sensitive nature of IVT and evaluate the safety of IVT in patients on oral anticoagulants.

KEYWORDS
emergency care, large vessel occlusion stroke, stroke, thrombolysis

1 | BACKGROUND

Intravenous thrombolysis (IVT) is a mainstay of care for acute ischemic stroke. In large vessel occlusion stroke (LVOS), IVT appears to have a synergistic effect with endovascular treatment (EVT).[1,2] However, many patients do not receive IVT as IVT has a long list of absolute and relative contraindications.[3]

1.1 | Importance

Prior studies have examined why patients have not received IVT. One study from Australia found that only one third of acute ischemic stroke patients presented within 4.5 hours of the onset of their stroke.[4] Of those patients, only 15% of patients received IVT. The most cited reasons for not administering IVT were minor and improving symptoms. Other studies inside and outside of the United States have shown similar results.[5,6]

LVOS patients typically present with more severe deficits, which should make them easier to identify. For patients with LVOS, endovascular treatment, which shows better results than medical management alone, is the mainstay of treatment.[7–13] Although there is some question of whether EVT coupled with IVT shows better results than IVT alone, recent evidence suggests a benefit of using IVT in addition to EVT.[1,2,14,15] The benefits of IVT may be higher if there is a delay to EVT of more than 30 minutes.[16] Administration of IVT may improve first-pass success rates and increase the pre-mechanical thrombectomy recanalization rate.[17,18] Given the synergistic effect of IVT and EVT it is critical that all LVOS patients who are eligible for IVT are treated. Compared to patients with non-LVO acute ischemic stroke, comparatively little is known about why IVT is not administered to patients with LVOS.

1.2 | Goals of this investigation

The goal of this investigation was to explore why IVT was not administered to a cohort of LVOS patients in the United States.

2 | METHODS

2.1 | Study design

This is an analysis of the Optimizing the Use of Prehospital Stroke Systems of Care-Reacting to Changing Paradigms (OPUS-REACH) registry. The methods of this registry have previously been described and published.[19]

2.2 | Selection of participants

The OPUS-REACH registry contains patients from 7 health systems and 8 endovascular centers (ESCs) who underwent EVT for LVOS between 2015 and 2020. Each site extracted patient data from their electronic medical record and submitted the deidentified data to *Blinded* University for analysis. Only patients who had their stroke after arrival at the hospital and those who arrived via mobile stroke unit were excluded from the analysis

We defined a hospital as a primary stroke center (PSC), acute stroke ready hospital (ASRH), thrombectomy capable center (TSC), or comprehensive stroke center (CSC) based on a variety of national, state, and local databases. First, we accessed the database of the Joint Commission (www.qualitycheck.org) and Det Norske Veritas to identify

THE BOTTOM LINE

In this cohort of 2043 large vessel occlusion stroke patients from 8 health systems, 60% of patients did not receive intravenous thrombolysis. The most common reasons that patients did not receive thrombolysis were hospital arrival >4.5 hours (57%) and oral anticoagulants (15.5%).

ESCs in New York, New Jersey, Delaware, and Pennsylvania.[20,21] We also accessed the state department of health websites for New York, New Jersey, Pennsylvania, and Delaware. [22–25] For the purposes of our analysis, we trichotomized hospitals into endovascular stroke centers (TSCs and CSCs), non-endovascular stroke centers (ASRHs and PSCs), and non-certified stroke centers.

Among the hospitals included in this investigation, EVT was the standard of care for patients with LVOS. All participating hospitals were ESC and maintained that status during the study period. In addition, IVT was the standard of care for all stroke patients presenting within 4.5 hours of stroke onset for both LVOS and non-LVOS.

2.3 | Exposure

The exposure of interest was the receipt of intravenous thrombolysis. Whether IVT was administered was determined by review of the electronic medical record or by the stroke center quality assurance database. All hospitals in the OPUS-REACH consortium are certified as ESCs by the American Heart Association and therefore required to record data according to the Get With the Guidelines (GWTG) program.[26] The GWTG database provides details of all stroke care given throughout a patient's hospitalization as well as follow-up outcome data. In the GWTG stroke database, if IVT is not administered to a patient, the reason for omitting IVT must be documented. The reasons that IVT was not administered are predefined in the data set and parallel the absolute and relative contraindications for IVT. If the reason for omitting IVT was not clear from the review of the GWTG data set, the site investigator reviewed the electronic medical record to determine why IVT was not administered.

2.4 | Data analysis

Descriptive summary statistics are presented as means and SDs for continuous variables and as frequencies with percentages for categorical variables. Two-sample *t* tests were used to compare continuous variables and the chi-square test was used to compare categorical variables between those who received IVT and those who did not receive EVT. We also compared patients across ESCs and non-ESCs. Univariate logistic regression was performed to establish potential factors that may contribute to administration of IVT. A priori, we defined a

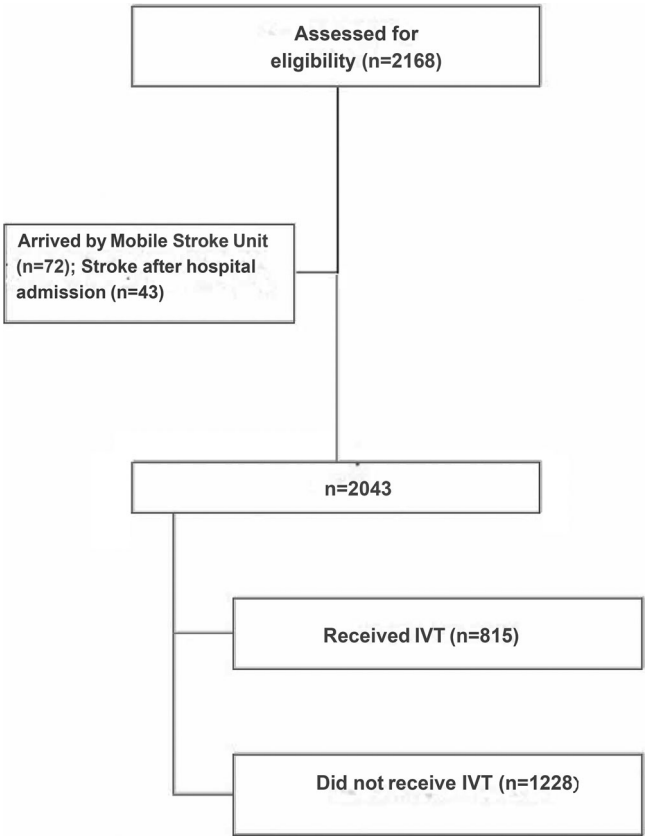

FIGURE 1 Enrollment flow diagram. Abbreviation: IVT, intravenous thrombolysis.

P value of <0.05 as significant in the univariate analysis. Multiple variable logistic regression was conducted to determine the association of variables to estimate an odds ratio (OR) for patients to receive IVT. The multiple variable regression model included age, baseline National Institutes of Health Stroke Scale (NIHSS) score, method of arrival, type of stroke center, and last known well to arrival at first hospital. Statistical analyses were performed with SAS Statistics Software, SAS 9.4 (SAS Institute, Cary, NC).

Institutional review boards of each of the 7 participating health systems approved this study. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

3 | RESULTS

Of the 2168 patients in the OPUS-REACH registry, 2043 patients were included in the final analysis. The patients were treated at 8 ESCs, 17 non-certified stroke centers, 1 ASRH, and 66 PSCs. Of these patients 60% did not receive IVT (Figure 1). The baseline characteristics of these patients are listed in Table 1. There were no differences in the rates of administration of IVT between sexes. Black patients were more likely to receive IVT than White patients (47.3% vs 38.6%) and there was no difference between Hispanic and non-Hispanic patients. The median age

TABLE 1 Baseline characteristics of patients ($n = 2043$).

Variable	Number missing	Overall ($n = 2043$)	IVT ($n = 815$)	No IVT ($n = 1228$)	*P* value
Female sex, *n* (%)		1046(51.3)	411(50.4)	635(51.7)	0.57
Race, *n* (%)	132				**0.023**
American Indian/Alaska Native		12(0.6)	3(0.4)	9(0.8)	
Asian/Native Hawaiian/Pacific Islander		16(0.8)	6(0.8)	10(0.9)	
Black or African American		283 (14.8)	134(17.5)	149(13)	
White		1583 (82.8)	611(80)	972(84.7)	
Other		17 (0.9)	10(1.3)	7(0.6)	
Hispanic ethnicity, *n*(%)	33	98 (4.9)	40(5)	58(4.8)	0.81
Median initial NIHSS score (IQR)	7	16 (10–21)	17(11.5–21)	15(10–21)	**0.005**
Median age (IQR)		72(61–82)	71(60–81)	73(63–83)	**0.001**
Hospital type, *n* (%)					**<0.0001**
Endovascular stroke center		1231 (60.2)	514 (63.1)	717 (58.4)	
Primary stroke center		753 (36.9)	268 (32.9)	485 (39.5)	
No stroke center certification		59 (2.9)	33 (4)	26 (2.1)	
Arrival method, *n* (%)	214				**0.004**
Emergency medical services		1748 (95.5)	718 (96.8)	1030 (93.8)	
Personally owned vehicle		92 (4.5)	24 (3.2)	68 (6.2)	
Median last known well to arrival at first hospital (minutes)	195	139 (59–411)	71 (45.5–126.5)	321 (107–645.5)	<0.0001

Abbreviations: IQR, interquartile range; IVT, intravenous thrombolysis.
Bold values indicates $P<0.05$.

of patients who received IVT was younger (71 years vs 73 years old) and had higher median NIHSS scores (17 vs 15). Surprisingly, the rate of administration of IVT was highest at non-certified stroke centers (55.9%) versus PSCs (35.7%) and ESCs (41.7%).

The most common reason for withholding IVT was arrival at the treating facility more than 4.5 hours after stroke onset (57.2%) (Table 2). Late presentations were more common at non-certified stroke centers followed by non-ESCs, and least common at ESCs. The second most frequent reason was active anticoagulant use (15.5%). The third and fourth most frequent reasons were "not documented" (5.7%) and "cannot determine eligibility" (2.7%). All other factors played minor roles in why IVT was not administered.

On multiple variable regression analysis, only 2 factors were associated with not receiving IVT: increasing age (OR 0.86; 95% confidence interval [CI] 0.78–0.93) and increasing time from last known well to arrival at the first hospital (OR 0.45; 95% CI 0.46–0.49) for each 100-minute increase (Figure 2). Differences in rates of IVT administration between levels of hospitals disappeared on multiple variable regression analysis.

4 | LIMITATIONS

This was a retrospective cohort study and is subject to the limitations of this type of study such as extraction errors entering data and missing data in the electronic medical record. The stroke patients from these 8 health systems may not be representative of patients from other parts of the United States or hospitals outside of the United States. In particular, we are limited to a set of patients all of whom were treated with EVT. In addition, only 2 patients from ASRHs were included in our data set. Finally, we did not stratify by hospitals as we had > 70 non-ESCs in our study, many of which contributed <10 patients to the study.

5 | DISCUSSION

Similar to prior studies, time from stroke onset to hospital arrival was the most significant factor that excluded patients from receiving IVT. This finding was surprising as patients had a median NIHSS score of 16, strokes that would have manifested with substantial neurologic deficits. This finding suggests there is still a lack of awareness among the public regarding stroke systems and the need for timely emergency department evaluation after stroke onset. However, we were unable to identify patients with wake-up strokes in our data set. This somewhat tempers our findings in that patients with wake-up stroke would not receive IVT because of vicissitude rather than lack of awareness.

Although current guidelines do not recommend administering IVT later than 4.5 hours after stroke onset, a 2020 meta-analysis suggested that a select population based on diffusion weight magnetic resonance imaging or computed tomography perfusion studies may

TABLE 2 Reasons why large vessel occlusion stroke patients did not receive IVT.

Variable *n* (%)	Overall (*n* = 1228)	ESC (*n* = 717)	Non-ESC (*n* = 485)	No certification (*n* = 66)	*P* value
Active anticoagulant use	190 (15.5)	118(16.5)	64(14.2)	3(11.5)	**0.49**
Age >80 years	10 (0.8)	6(0.9)	4(0.8)	0	**0.90**
Computed tomography showed multilobar infarction	9 (0.7)	5(0.7)	4(0.8)	0	**0.88**
Cannot determine eligibility	33 (2.7)	20(2.8)	13(2.7)	0	**0.69**
History of gastrointestinal bleeding	9 (0.6)	2(0.3)	5(1.0)	0	**0.22**
History of intracranial bleed	24 (2.0)	16(2.2)	7(1.4)	1(3.8)	**0.49**
History of prior stroke and diabetes	7 (0.6)	4(0.6)	3(0.6)	0	**0.92**
Known intracranial arteriovenous malformation	13(1.1)	8(1.2)	4(0.8)	0	**0.67**
Major surgery	14 (1.1)	8(1.1)	6(1.2)	0	**0.84**
National Institutes of Health Stroke Scale score > 25	19 (1.2)	12(1.7)	6(1.2)	1(3.8)	**0.53**
Recent neurosurgery/head trauma	31 (2.5)	22(3.1)	9(1.9)	0(0.0)	**0.30**
Not documented	70 (5.7)	30(4.2)	38(7.8)	2(7.7)	**0.025**
Only minor or rapidly improving symptoms	11 (0.9)	8(1.1)	3(0.6)	0(0.0)	**0.59**
Recent arterial puncture	1 (0.1)	0(0.0)	1(0.2)	0(0.0)	**0.46**
Other	29 (2.4)	22(3.1)	7(1.4)	0(0.0)	**0.14**
Refused intravenous thrombosis	10 (0.8)	6(0.9)	3(0.7)	1(1.5)	**0.75**
Seizure at stroke onset	2 (0.2)	1(0.1)	1(0.2)	0(0.0)	**0.94**
Stroke onset > 4.5 hours	702(57.2)	391(54.5)	292(60.2)	19(73.1)	**0.038**
Uncontrolled hypertension	11(0.9)	7(1.0)	4(08)	0(0.0)	**0.85**
Chronic thrombocytopenia	2 (0.2)	0	2(0.4)	0	**0.22**

Abbreviation: ESC, endovascular center. IVT, intravenous thrombolysis.
Bold values indicates $P<0.05$.

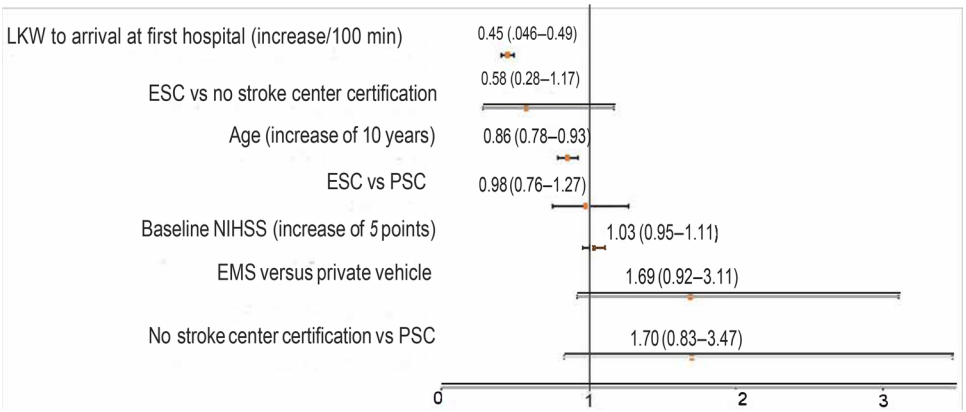

FIGURE 2 Odds ratios for receipt of intravenous thrombolysis, multivariable regression model includes age, baseline NIHSS, method of arrival, type of stroke center, and last known well to arrival at first hospital. Abbreviations: ESC, endovascular center; EMS, emergency medical services; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale score; PSC, primary stroke center.

benefit from later administration of IVT.[27] Among 414 patients with wake-up strokes or who were between 4.5 and 9 hours from stroke onset, patients who received IVT had better functional outcomes at 3 months, though greater rates of symptomatic intracerebral hemorrhage. Current studies are exploring whether IVT is safe and effective beyond 4.5 hours.[28]

The second most common reason that stroke patients did not received IVT was that patients were taking anticoagulants. Concordant with the 2018 American Heart Association guidelines that give a Class III (potentially harmful) recommendation against empirically treating patients on direct oral anticoagulants (DOACs) with IVT.[3] However, if there is laboratory confirmation that the patient is not coagulopathic or the internationalized normal ratio for patients on warfarin is <1.7, IVT may be considered. A meta-analysis published in 2020 found that DOACs did not appear to increase the risk of intracranial hemorrhage after administration of IVT.[29] A more recent analysis of 163,000 patients found no increased rate of hemorrhage when patients on novel oral anticoagulants were treated with intravenous alteplase.[30] Further research and discussion should focus on the safety of administering IVT to patients on anticoagulation.

The reasons that 5.7% of patients did not receive IVT were not documented. This was least common at ESCs and equally common non-ESCs and non-certified stroke centers. As non-ESCs maintain stroke databases for their stroke certifications, more complete documentation of why patients did not receive IVT may represent an area for improvement and lead to increased administration of IVT.

On multiple variable analysis, 2 factors were associated with not receiving IVT: age and time from stroke onset to arrival at the hospital. Not surprisingly, for each 100-minute delay from stroke onset to IVT, the odds of receiving IVT decreased by 55%. As IVT is a time-dependent medication, this finding is expected. Additionally, despite several studies showing that IVT benefits patients older than 80 and even 90 years of age,[31,32] for each increase of 10 years in age, the odds of receiving IVT was reduced by 14% suggesting that IVT may have been inappropriately withheld because of age. Consideration should be given to removing age-based relative contraindications from IVT administration guidelines.

This is one of the first large multicenter cohort studies examining why LVOS patients in the United States do not receive IVT. Like prior studies, the most frequent reason for exclusion from IVT was a time of onset to presentation of greater than 4.5 hours. The second most common reason was anticoagulation. As IVT increases functional outcomes in LVOS, efforts must be made to increase public awareness of the time-sensitive nature of IVT, although the magnitude of this effect is blunted by patients with wake-up strokes who would be unable to receive IVT under any circumstance. Future research should also look at the safety of intravenous thrombolysis in patients on warfarin or other DOACs.

AUTHOR CONTRIBUTIONS

Ethan S. Brandler: Conceptualization, data collection, data analysis, critical review and evaluation of results, primary authorship of the paper; Derek L. Isenberg: Conceptualization, data collection, data analysis, critical review and evaluation of results, primary authorship of the paper, study supervision, procurement of grant or other funding; Joseph Herres: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper; Huaqing Zhao: Data analysis, critical review and editing of the paper; Chadd K. Kraus: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper; Daniel Ackerman: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper; Adam Sigal: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper; Alexander Kuc: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper; Jason T. Nomura: Conceptualization, data collection, critical review and evaluation of results, review and editing of the paper, procurement of grant or other funding; Susan Wojcik: Data collection, critical review and evaluation of results, review and editing of the paper; Michael T. Mullen: Review and editing of the paper, critical review and evaluation of results; Nina T. Gentile: Conceptualization, critical review and evaluation of results, study supervision, review and editing of the paper

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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