ORIGINAL RESEARCH

Comparative Effectiveness of Standard Care With IV Thrombolysis Versus Without IV Thrombolysis for Mild Ischemic Stroke

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***Background*—**One third of patients presenting with initially mild strokes have unfavorable outcomes, and the efficacy of intravenous thrombolysis (IVT) in this population has not been proven. This study aimed to evaluate the comparative effectiveness of standard care with IVT versus without IVT in mild stroke patients.

***Methods and Results*—**Using a multicenter stroke registry database, we identified patients with acute ischemic stroke who presented within 4.5 hours of symptom onset and had initial National Institutes of Health Stroke Scale scores ≤5. Multivariable logistic analysis and propensity score matching were used to adjust for baseline imbalances between the patients who did and did not receive IVT. Adjusted odds ratios and 95% CIs of IVT were estimated for 3-month modified Rankin Scale scores of 0 to 1 and symptomatic. Of 13 117 patients with stroke who were hospitalized between April 2008 and May 2012, 1386 met the eligibility criteria, and 194 (14.0%) were treated with IVT. For a modified Rankin Scale of 0 to 1 at 3 months, the adjusted odds ratios were 1.96 (95% CI, 1.28 to 3.00; *P*=0.002) by multivariable logistic analysis and 1.68 (1.10 to 2.56; *P*=0.02) by propensity score matching analysis, respectively. There was a statistically nonsignificant excess of symptomatic hemorrhagic transformation (odds ratios=3.76 [0.95 to 16.42; *P*=0.06] and 4.81 [0.84 to 49.34; *P*=0.09]), respectively.

***Conclusions*—**In this observational registry-based study, standard care with IVT is more effective than not receiving IVT in mild ischemic stroke patients, and there is a statistically nonsignificant risk of symptomatic hemorrhagic transformation. **(*J Am Heart Assoc*. 2015;4:e001306 doi: 10.1161/JAHA.114.001306)**

Key Words: ischemic stroke • outcome • thrombolysis

Most pivotal stroke trials for intravenous thrombolysis (IVT) excluded patients presenting with mild symptoms,[1–4] and current stroke guidelines have only begun to consider IVT administration for mild stroke.[5,6] However, approximately one third of patients who were not treated with IVT due to mild stroke symptoms were reported to have poor outcomes.[7–9]

Although there has been no published large-scale randomized clinical trial for this specific patient subgroup, several studies have explored the efficacy and safety of IVT in this population, but the results have been inconsistent.[10–15] Moreover, these studies have had limitations such as a small sample size,[10,13–15] historical controls[15] or no controls[13] as

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the comparator group, only discharge outcomes,[11] or insufficient adjustments for baseline imbalances between treatment and control groups.[10–15]

In the absence of high-level evidence from randomized controlled clinical trials, observational data from a large clinical registry can be useful if confounding due to baseline imbalance can be controlled adequately.[16] Using a multicenter stroke registry database, our study aimed to compare the effectiveness and safety of standard care with IVT and without IVT in patients with ischemic stroke who presented with mild neurologic deficits (National Institutes of Health Stroke Scale (NIHSS) score ≤5) within 4.5 hours of stroke onset.

Methods

Study Subjects

This study was a retrospective analysis based on the Clinical Research Center for Stroke-5th division registry database. The Clinical Research Center for Stroke-5th division registry is a prospective web-based registry of consecutive patients with acute ischemic stroke who were admitted to 12 university hospitals or regional stroke centers in the Republic of Korea since 2008.[17] Using the registry database, we identified study subjects who met the following inclusion criteria: age ≥18 years; evidence of acute ischemic stroke on neuroimaging; time interval from last seen normal to hospital arrival ≤4.5 hours; and baseline NIHSS score ≤5. Patients who had a prestroke modified Rankin Scale (mRS) >0, received IVT >4.5 hours from last witnessed as being normal, were treated with IVT before arriving at the participating centers, were treated with endovascular therapy, or for whom information on 3-month mRS was not available were excluded.

Data Collection

Clinical information was obtained directly from the registry database or by manual review of medical records. Using a standardized case record form and according to predefined operational guidelines, participating centers were required to register all consecutive patients with stroke or transient ischemic attack hospitalized within 7 days of symptom onset. Details of the registry database are published elsewhere.[17]

Collection of clinical information for the purpose of monitoring and improving the quality of stroke care was approved by the local institutional review boards of all participating centers of the Clinical Research Center for Stroke-5th division. A waiver of informed consent from study subjects was granted mainly because of study subject anonymity, the retrospective nature of the data collection process despite the prospective study design, and the minimal risk to participating subjects. Use of the registry database and additional collection of information by chart review for conducting and publishing this study was approved by the institutional review boards.

Stroke Classification and Criteria for Symptomatic Stenosis

Ischemic stroke was classified as large-artery atherosclerosis (LAA), small-vessel occlusion (SVO), cardioembolism, stroke of undetermined etiology (UDE), or stroke of other determined etiology according to the Trial of Org 10172 in Acute Stroke Treatment criteria[18] with minor modifications. The main modifications were (1) branch atheromatous diseases without evidence of cardiac embolism as LAA rather than UDE; and (2) infarctions at anterior choroidal artery territory, single territory of cerebellum, or medullar oblongata without evidence of cardiac embolism as LAA since those infarctions are not usually caused by SVO.[19–22]

Symptomatic stenosis or occlusion of the major arteries was assessed using computed tomography angiography, magnetic resonance angiography, or conventional catheter angiography. For intracranial arteries, it was defined as >50% stenosis of the artery compared with proximal or distal normal segment.[23]

Outcome Measurements

The primary outcome was a favorable functional outcome as judged by a mRS of 0 to 1 at 3 months. Safety measures included mortality at 3 months and symptomatic hemorrhagic transformation (HT). Symptomatic HT was defined according to the European Cooperative Acute Stroke Study 3 protocol.[2]

Investigators and research nurses who participated in the registry program were certified to administer the NIHSS and mRS after successfully completing a web-based training program provided by the Clinical Research Center for Stroke (http://www.stroke-crc.or.kr).

Statistical Analysis

Patients who met the eligibility criteria were divided into standard care with IVT and standard care without IVT, which were compared with respect to baseline characteristics and outcomes.

Baseline characteristics of the 2 groups were expected to differ substantially. To overcome those differences, we adopted the following strategies:

1. On multivariable logistic regression, variables with *P* values <0.2 on comparisons of baseline characteristics between the 2 groups were included as covariates. Age, sex, and baseline NIHSS score were entered into the models regardless of their *P* values.

2. Propensity scores (PSs) were generated to estimate the individual probability of a patient receiving IVT instead of the standard care without IVT based on his or her baseline characteristics.[24] Thirty variables were used to calculate the PS, which included the following factors: demographic and admission characteristics, diagnostic study and laboratory results, vascular risk factors, stroke-specific characteristics, and prestroke medications. After the PS was obtained, 1 case in the IVT group was matched to 2 controls in the standard care without IVT group within a 0.2 times SD of the logit of PS using the nearest neighbor matching according to the caliper method. Standardized differences of the mean (SDM) were used to check for balance between the cases and controls after matching. For the matched data set, an outcome analysis was performed using a generalized estimation equation method with a logit link.
3. Further adjustments were made for variables with absolute values of standardized differences of the mean >0.1 in the PS-matching analysis.

For the symptomatic HT and the mortality at 3 months, exact logistic regression models were used due to the small number of events. Statistical validity of the regression models was examined using C-statistic and Hosmer & Lemeshow goodness-of-fit tests.

All of these results are presented as odds ratios and 95% CIs of IVT compared with no IVT for the 3 clinical outcomes: mRS scores of 0 to 1 at 3 months, symptomatic HT, and death at 3 months. Significance levels were set at a 2-tailed $P<0.05$. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Since NIHSS is not a disability score and individual items can produce quite a different impact on functional disability, we tested the robustness of the study results using other criteria for identifying mild stroke patients with high risk for developing future disability. First, we repeated the analysis after excluding the study subjects who met the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) stroke study's exclusion criteria for minor stroke.[14] We noted that, in the NINDS tPA study, minor stroke was defined as isolated symptoms of sensory loss, facial weakness, ataxia, dysarthria, or no measurable deficit on the NIHSS (ie, NIHSS=0). Second, we performed the analysis after applying the definition of disabling deficits as suggested by the REexamining Acute Eligibility for Thrombolysis (TREAT) Task Force.[25] The following criteria were used to define disabling deficits: complete hemianopsia (≥2 on the NIHSS item 3), severe aphasia (≥2 on NIHSS item 9), visual or sensory extinction (≥1 on NIHSS item 11), or any weakness limiting sustained effort against gravity (≥2 on NIHSS item 5 or 6).

We also investigated whether tPA dose influenced outcomes by performing the analysis after excluding patients who received a tPA dose of 0.6 mg/kg instead of a standard dose of 0.9 mg/kg. Finally, to evaluate the efficacy of IVT on mild stroke caused by SVO that showed an efficacy signal in the original NINDS trial, we also performed the analysis on a separate SVO cohort.

Results

Between April 2008 and May 2012, 13 116 patients were hospitalized with acute stroke at 1 of the 12 participating centers. Of this group, 1384 met the eligibility criteria (Figure 1). Missing values for total cholesterol (2.0%) and initial fasting glucose (4.8%) were substituted with median group values.

Of the 1384 study subjects, 53% were ≥65 years and 63% were men. Hypertension was the most frequent vascular risk factor (65.8%), followed by smoking (42.6%), hyperlipidemia (33.5%), and diabetes mellitus (25.9%). The median baseline NIHSS score was 2 (interquartile range, 0 to 3), and large-artery atherosclerosis (33.2%) was the most common stroke subtype.

One-hundred ninety-four patients (14.0%) were treated with IVT. The proportions of patients receiving IVT in the 12 participating centers ranged from 0% to 35%. Among those 194 patients, the dose of tPA was 0.9 mg/kg in 74.2% and 0.6 mg/kg in 25.8%; median onset-to-needle time was 132 minutes (interquartile range, 102 to 174 minutes); and median door-to-needle time was 47 minutes (interquartile range, 38 to 63 minutes).

Compared with the patients without IVT, the patient treated with IVT was more likely to arrive at the hospital earlier and have higher baseline NIHSS scores but was less likely to receive antiplatelet therapy prior to stroke onset. Table 1 shows the 30 variables that were used to estimate the PS for cases and controls. Using these PSs, 144 IVT-treated patients were matched to 224 untreated patients (n=368; 1:1 in 64 pairs and 1:2 in 80 pairs). The unmatched 1016 patients were excluded in the following PS analysis. Imbalances in the distribution of PSs between the patients with IVT and without IVT were largely rectified by matching (Figure 2). However, the absolute values of standardized differences of the mean for onset to arrival time, clear onset, baseline NIHSS, and magnetic resonance imaging as initial neuroimaging were still ≥0.1 despite PS matching.

On the unadjusted analysis, the proportions of mRS scores of 0 to 1 at 3 months did not differ between the patients with IVT and without IVT (70.6% versus 75.3%, $P=0.165$). However, multivariable logistic regression analysis showed a statisti-

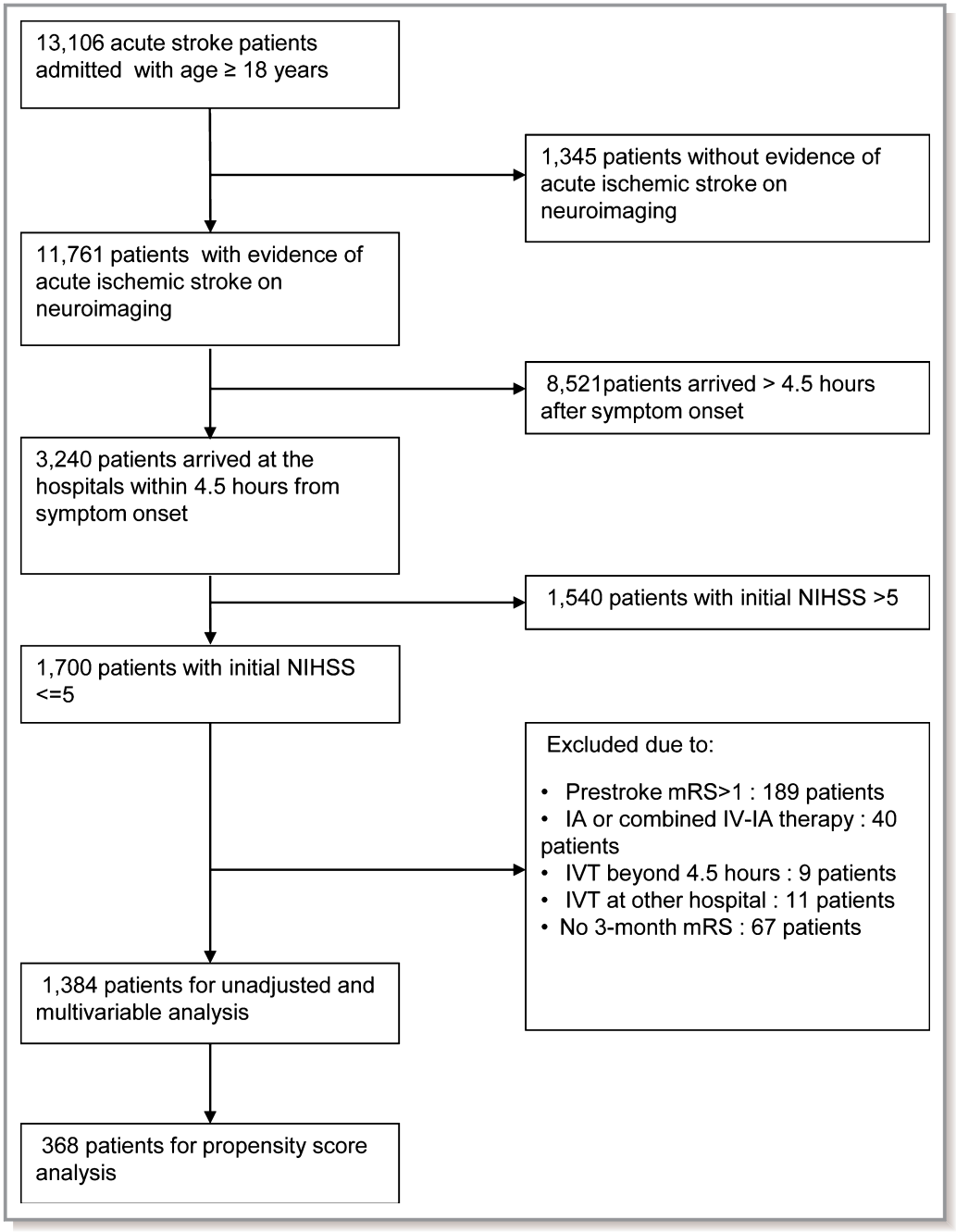

Figure 1. Enrollment of the study subjects. IA indicates intraarterial; IV-IA, intravenous-intraarterial; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

cally significant association of IVT with favorable functional outcome at 3 months (odds ratio 1.96; 95% CI, 1.28 to 3.00; *P*=0.002) (Table 2). After the PS matching, the effect of IVT on functional outcome remained significant (1.68; 1.10 to 2.56; *P*=0.02), and additional adjustments for variables whose absolute standardized differences of the mean were >0.1 did not affect the statistical significance of that association (1.88; 1.19 to 2.96; *P*=0.01) (Figure 3).

The symptomatic HT rate was 1.0% (n=14) in all the study subjects: 4.1% (n=8) in the patients with IVT and 0.5% (n=6) in those without IVT (*P*<0.001). IVT increased a risk of symptomatic HT about 8 times, although the multivariable logistic regression and PS-matched analyses showed that the increase was not statistically significant. The mortality at 3 months was 1.8% (n=25) in all the study subjects: 1.0% (n=2) in the patients with IVT and 1.9% (n=23) in the patients without IVT (*P*=0.39). IVT did not significantly affect the mortality rate at 3 months (Table 2). Thus, both the symptomatic HT and mortality rates are based on a relatively small number of outcome events.

Table 1. Baseline Characteristic of 1384 Patients With Stroke and 368 Matched Patients

	Before PS Matching			After PS Matching		
	No IVT (n=1190)	IVT (n=194)	SDM*	No IVT (n=224)	IVT (n=144)	SDM*
Demographics						
Age	64±13	63±13	0.06	63.8±14.0	63.9±13.7	0.001
Male	752 (63.2)	126 (65.0)	0.04	153 (68.3)	93 (64.6)	0.08
Admission characteristics						
Onset to arrival time, minutes†	114 (60 to 180)	78 (48 to 108)	0.66	78 (42 to 144)	78 (54 to 120)	0.11
Clear onset	1119 (94.0)	183 (94.3)	0.01	205 (91.5)	136 (94.4)	0.12
Diagnostic workup						
CT	613 (51.5)	129 (66.5)	0.31	141 (62.9)	93 (64.6)	0.03
CT angiography	419 (35.2)	112 (57.7)	0.46	113 (50.4)	78 (54.2)	0.08
MRI	1042 (87.6)	153 (78.9)	0.23	193 (86.2)	118 (81.9)	0.12
Risk factors						
Hypertension	794 (66.7)	117 (60.3)	0.13	132 (58.9)	86 (59.7)	0.02
DM	318 (26.7)	41 (21.1)	0.13	51 (22.8)	32 (22.2)	0.01
Dyslipidemia	406 (34.0)	58 (29.9)	0.09	60 (26.8)	42 (29.2)	0.07
Smoking	508 (42.7)	81 (41.8)	0.02	106 (47.3)	63 (43.8)	0.05
Atrial fibrillation	205 (17.2)	32 (16.5)	0.02	43 (19.2)	23 (16.0)	0.09
History of stroke	174 (14.6)	20 (10.3)	0.02	25 (11.2)	16 (11.1)	0.002
History of CAD	101 (8.5)	15 (7.7)	0.13	20 (8.9)	12 (8.3)	0.02
Laboratory findings						
SBP, mm Hg	152±28	155±29	0.10	152±27	151±28	0.03
Hemoglobin, g/dL	13.9±1.8	14.0±1.6	0.05	14.0±1.7	13.9±1.6	0.07
Platelet, k/mm^3	233±76	231±69	0.03	230±78	232±68	0.02
Fasting glucose, mg/dL	178±40	183±36	0.15	111±34	108±38	0.08
BUN	16.5±8.7	15.8±5.3	0.09	16.7±9.2	16.1±5.4	0.09
Creatinine	1.01±0.99	0.98±0.71	0.04	0.98±0.75	1.00±0.80	0.03
Total cholesterol, mg/dL	113±43	107±36	0.14	181±46	180±36	0.03
Stroke characteristics						
Baseline NIHSS score†, median (IQR)	1 (0 to 3)	4 (3 to 5)	1.57	3 (2 to 4)	4 (3 to 4)	0.17
Stroke subtype‡						
LAA	386 (32.4)	74 (38.1)	0.12	85 (37.9)	55 (38.2)	0.005
SVO	243 (20.4)	30 (15.5)	0.13	31 (13.8)	22 (15.3)	0.04
CE	243 (20.4)	39 (20.1)	0.008	50 (22.3)	29 (20.1)	0.05
UDE or ODE	318 (26.7)	51 (26.3)	0.01	58 (25.9)	38 (26.4)	0.01
SYSO§	411 (34.5)	77 (39.7)	0.11	94 (42.0)	60 (41.7)	0.006
Prestroke medication						
Antiplatelet†	356 (29.9)	43 (22.2)	0.18	60 (26.8)	36 (25.0)	0.04
Anticoagulant	59 (5.0)	9 (4.6)	0.02	11 (4.9)	7 (4.9)	0.002
Statin	183 (15.4)	23 (11.9)	0.10	24 (10.7)	18 (12.5)	0.06

Values are number of patients (%), mean±SD or median (interquartile range [IQR]) unless otherwise indicated. BUN indicates blood urea nitrogen; CAD, coronary artery disease; CE, cardioembolism; CT, computerized tomography; DM, diabetes mellitus; IVT, intravenous thrombolysis; LAA, large-artery atherosclerosis; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiologies; PS, propensity score; SBP, systolic blood pressure; SDM, standardized difference in the mean; SVO, small-vessel occlusion; SYSO, symptomatic stenosis or occlusion of the major cerebral arteries; UDE, stroke of undetermined etiology.

*Absolute value of SDM of each variable between treated and untreated subjects.

†$P<0.05$; P-values are calculated by Pearson χ^2 test, Fisher's exact test, Student t test or Wilcoxon rank sum test as appropriate.

‡Stroke subtypes were determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[18]

§SYSO was defined as >50% stenosis of symptomatic artery confirmed by CT angiography or MR angiography in at least 1 of the intra- or extracranial arteries.[23]

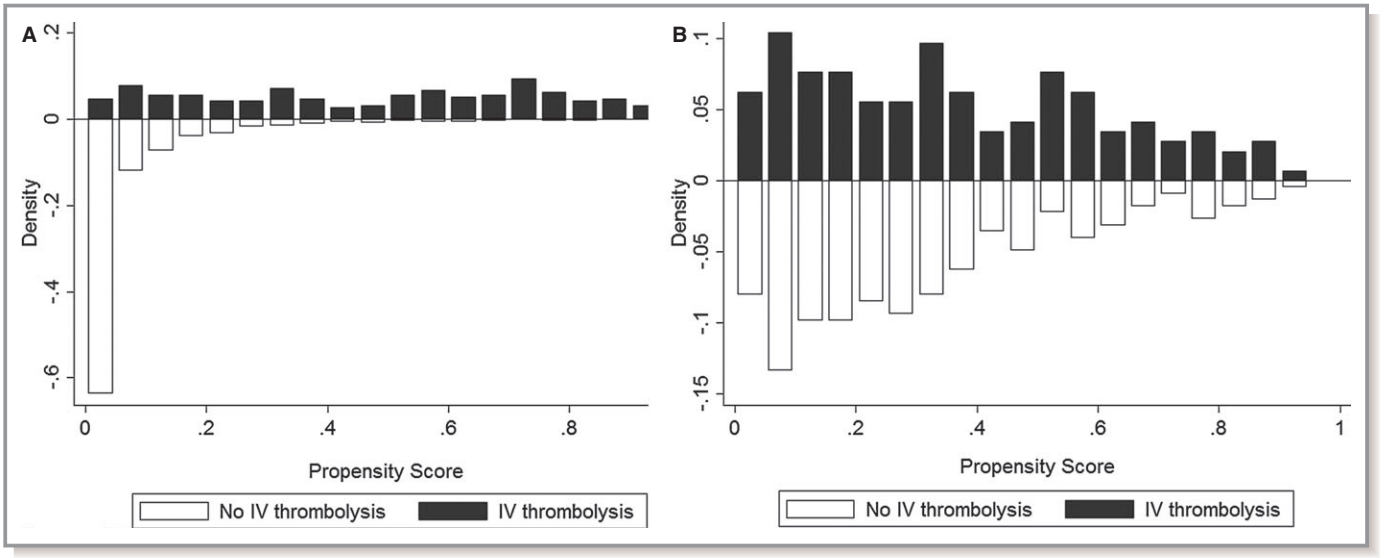

Figure 2. Distribution of propensity scores before (A) and after (B) matching. IV indicates intravenous.

Of the 1384 study subjects, 570 (41.2%) met at least 1 NINDS tPA trial minor stroke criterion (sensory loss [n=43], facial weakness [n=16], ataxia [n=42], dysarthria [n=109], and no measurable deficit on the NIHSS [n=361]). However, of the 194 patients treated with IVT, only 10 (5.2%) met at least 1 minor stroke criterion. The results of the analysis excluding those 570 subjects did not differ from those of the original analysis (Table 3). A total of 123 (8.9%) among 1384 patients met the disability criteria according to the REexamining Acute Eligibility for Thrombolysis Task Force. Among them, 48 patients (39.0%) were treated with IVT. The proportions of favorable functional outcome at 3 months and the symptomatic HT did not differ significantly between the patients with IVT and without IVT (Table 4). Another sensitivity analysis performed after excluding patients who received low-dose tPA (0.6 mg/kg) showed significant improvement of functional outcome at 3 months, a nonsignificant increase of symptomatic HT, and a nonsignificant reduction of death at 3 months (Table 5). Lastly, in a separate cohort consisting of patients presenting with SVO (n=273), the proportions of favorable functional outcome at 3 months did not differ significantly between the patients with IVT and without IVT (Table 6).

Discussion

Fourteen percent of the 1384 eligible subjects were treated with IVT, and this statistic increased to 23% when we excluded those who met the NINDS trial minor stroke criteria.

Table 2. Odds Ratios (OR) for Clinical Outcomes by Standard Care With IV Thrombolysis Compared Without IV Thrombolysis

	mRS Score of 0 to 1 at 3 Months			Symptomatic HT*			Death at 3 Months*		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Crude analysis	0.79	0.56 to 1.10	0.17	8.47	2.54 to 29.95	<0.001	0.53	0.12 to 2.26	0.39
Multivariable analysis[†]	1.96	1.28 to 3.00	0.002	3.76	0.95 to 16.42	0.06	0.36	0.07 to 1.80	0.21
PS matching[‡]	1.68	1.10 to 2.56	0.02	4.81	0.84 to 49.34	0.09	0.38	0.08 to 1.84	0.23
PS matching with additional adjustments[§]	1.88	1.19 to 2.96	0.01	4.27	0.76 to 43.60	0.12	0.39	0.08 to 1.79	0.22

BUN indicates blood urea nitrogen; CT, computed tomography; DM, diabetes mellitus; HT, hemorrhagic transformation; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin disability scale; NIHSS, National Institutes of Health Stroke Scale; PS, propensity score; SBP, systolic blood pressure; SYSO, symptomatic stenosis or occlusion of the major cerebral arteries.

*For the symptomatic HT and 3-month mortality, exact logistic regression analyses were performed. C-statistics and *P*-values for Hosmer-Lemershow goodness-of-fit test in the multivariable analyses were 0.81 and 0.21 for the symptomatic HT; 0.84 and 0.86 for the 3-month mortality, respectively.

[†]Adjusted for age, sex, baseline NIHSS score, onset to arrival time, hypertension, DM, history of stroke, antiplatelet, SBP, fasting glucose, BUN, total cholesterol, CT, CT angiography, MRI, and SYSO in mRS score outcome; adjusted for age, sex, and baseline NIHSS score in symptomatic HT; adjusted for age, sex, baseline NIHSS score, onset to arrival time, hypertension, DM, history of stroke, antiplatelet, SBP, fasting glucose, BUN, total cholesterol, CT, CT angiography, MRI, and SYSO in 3-month death.

[‡]PS-matched sample included 144 pairs with 1:1 in 64 pairs and 1:2 in 80 pairs.

[§]Adjusted for baseline NIHSS score, onset to arrival time, MRI, and clear onset in mRS outcome; adjusted for age, sex, baseline NIHSS score, onset to arrival time, and fasting glucose in symptomatic HT; and adjusted for baseline NIHSS score, onset to arrival time, MRI, and clear onset in death at 3 months.

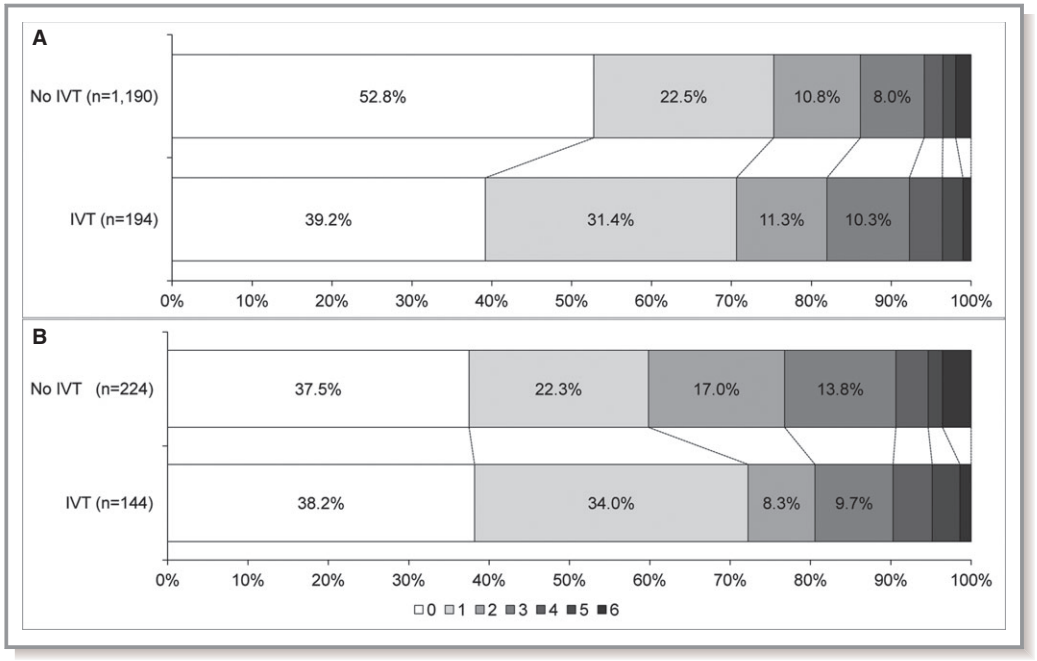

Figure 3. Distribution of 3-month modified Rankin Scale score before (A) and after (B) propensity score matching. IVT indicates intravenous thrombolysis.

The results of the analyses suggest that standard care with IVT may be advantageous over care without IVT for achieving a favorable global outcome at 3 months as judged by the mRS score, but there was a small increased risk of symptomatic HT, although it was statistically insignificant.

Although several studies have suggested more favorable outcomes at 3 months or discharge in mild stroke patients treated with IVT compared with patients without IVT,[11,12,15] other studies reported no significant improvement of outcome with IVT administration.[10,14] Recently, a large observational study using the Austrian stroke unit registry database reported a better outcome at 3 months in mild stroke patients treated with IVT compared with matched controls who were not treated with tPA (odds ratio 1.49; 95% CI, 1.17 to 1.89).[26] In this study, odds ratios for a 3-month mRS score of 0 to 1 were 1.96 on the multivariable logistic regression analysis and 1.88 on the PS-matched analysis with additional adjustments for imbalances in variables that were not resolved with PS matching. Although Asian patients may be different from patients from Western populations with respect

Table 3. Odds Ratios (OR) for Clinical Outcomes by Standard Care With IV Thrombolysis Compared to Without IV Thrombolysis After Applying the NINDS tPA Stroke Study's Minor Stroke Exclusion Criteria

	mRS 0 to 1 at 3 Months			Symptomatic HT*			Death at 3 Months*		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Crude analysis	1.15	0.81 to 1.64	0.43	5.67	1.61 to 22.30	0.01	0.40	0.09 to 1.73	0.22
Multivariable analysis†	1.90	1.22 to 2.96	0.005	3.76	0.94 to 16.91	0.06	0.40	0.08 to 2.12	0.28
PS matching‡	1.70	1.10 to 2.63	0.02	3.97	0.64 to 42.26	0.17	0.31	0.04 to 2.58	0.28
PS matching with additional adjustments§	1.93	1.20 to 3.11	0.01	3.68	0.68 to 19.92	0.13	0.29	0.03 to 2.54	0.26

OR for IV thrombolysis. CT indicates computerized tomography; DM, diabetes mellitus; HT, hemorrhagic transformation; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; PS, propensity score; tPA, tissue plasminogen activator.
*For the symptomatic HT and 3-month mortality, exact logistic regression analyses were performed.
†Adjusted for age, sex, hypertension, DM, history of stroke, antiplatelet, fasting glucose, total cholesterol, CT, CT angiography, MRI, baseline NIHSS score, and onset to arrival time in mRS outcome; adjusted for age, sex, and baseline NIHSS score in symptomatic HT; and adjusted for age, sex, hypertension, DM, history stroke, antiplatelet, fasting glucose, total cholesterol, CT, CT angiography, MRI, baseline NIHSS score, and onset to arrival time.
‡PS-matched sample included 133 pairs with 1:1 in 60 pairs and 1:2 in 73 pairs.
§Adjusted for age, sex, baseline NIHSS score, onset to arrival time, and fasting glucose in mRS outcome; adjusted for age, sex, baseline NIHSS score, and onset to arrival time in symptomatic HT; and adjusted for age, sex, baseline NIHSS score, and onset to arrival time in death at 3 months.

Table 4. Odds Ratios (OR) for Clinical Outcomes by Standard Care With IV Thrombolysis Compared to Without IV Thrombolysis After Applying the TREAT Task Force's Disability Criteria

	mRS 0 to 1 at 3 Months			Symptomatic HT*			Death at 3 Months*		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Crude analysis	1.36	0.64 to 2.87	0.42	1.60	0.31 to 8.27	0.58	0.51	0.09 to 1.73	0.98
Multivariable analysis†	2.15	0.75 to 6.21	0.16	1.71	0.17 to 16.67	0.91	0.54	0.08 to 2.12	0.60
PS matching‡	1.20	0.33 to 4.35	0.78	4.13	0.60 to Infinity	0.23	1.00	0.04 to 2.58	1.00
PS matching with additional adjustments§	0.98	0.25 to 3.82	0.97	—	—	—	—	—	—

OR for IV thrombolysis. BUN indicates blood urea nitrogen; CT, computerized tomography; DM, diabetes mellitus; HT, hemorrhagic transformation; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PS, propensity score; SBP, systolic blood pressure; SYSO, symptomatic stenosis or occlusion of the major cerebral arteries; TREAT, REexamining Acute Eligibility for Thrombolysis.

*For the symptomatic HT and 3-month mortality, exact logistic regression analyses were performed.

†Adjusted for age, sex, baseline NIHSS score, onset to arrival time, hypertension, DM, history of stroke, antiplatelet, SBP, fasting glucose, BUN, total cholesterol, CT, CT angiography, MRI, and SYSO.

‡PS-matched sample included 24 pairs.

§Adjusted for age, sex, baseline NIHSS score, and onset to arrival time.

to ischemic stroke mechanisms and efficacy and safety profiles of IVT,[27–29] this study demonstrated that Korean patients are similar to Austrian patients in relation to the effectiveness of IVT for mild stroke. Furthermore, the findings did not change by exclusion of patients treated with lower-dose tPA. This study, however, was not intended to examine the effectiveness of low-dose tPA in mild stroke patients. A randomized controlled trial for comparison of the lower-dose tPA with standard-dose tPA in acute ischemic stroke within 4.5 hours of symptom onset is ongoing [http://clinicaltrials.gov/show/NCT01422616].[30]

In spite of overall effectiveness and safety of IVT for mild stroke patients, it is still uncertain which criteria should be used for selecting candidates for IVT among mild stroke patients. Since the majority of research on mild stroke patients incorporates initial NIHSS score for the definition of mild stroke, the NIHSS score would be a convenient tool to use for selecting IVT candidates among patients with mild stroke. However, at this time there is no proven cutoff point of total NIHSS score for thrombolytic therapy in this group.[26,31] Due to a lack of statistical power, we could not examine whether the efficacy and safety of IVT might change by applying different cutoff points of the NIHSS score in mild stroke patients.

Alternatively, we performed sensitivity analyses using 2 different qualitative criteria to identify and thus exclude patients with very minor stroke symptoms. In the first sensitivity analysis, we applied minor stroke criteria that were used in the original NINDS tPA trial.[14] The analysis included 814 patients (184 patients with IVT) and showed a similar magnitude of effectiveness of IVT to those observed in our original data set. The second sensitivity analysis used the disability criteria of the REexamining Acute Eligibility for Thrombolysis Task Force,[25] but did not demonstrate the effectiveness of IVT. It is noteworthy that only 123 patients met the criteria (48 patients with IVT), and as a result both multivariable and PS matching analyses showed much wider CIs compared to those of the original dataset. Due to a small

Table 5. Odds Ratios (OR) for Clinical Outcomes by Standard Care With IV Thrombolysis Compared to Without IV Thrombolysis After Excluding Patients Who Received the Low-Dose tPA (0.6 mg/kg)

	mRS Score of 0 to 1 at 3 Months			Symptomatic HT*			Death at 3 Months*		
	OR	95% CI	*P* Value	OR†	95% CI	*P* Value	OR†	95% CI	*P* Value
Crude analysis	0.88	0.60 to 1.31	0.53	7.08	1.69 to 28.24	0.007	0.72	0.08 to 2.94	0.97
PS matching‡	1.81	1.06 to 3.08	0.03	6.14	0.93 to Infinity	0.116	0.31	0.01 to 2.82	0.50
PS matching with additional adjustments†	2.00	1.14 to 3.51	0.016	3.79	0.48 to Infinity	0.29	0.48	0.01 to 5.03	0.89

PS-matched sample included 117 pairs with 1:1 in 50 pairs and 1:2 in 67 pairs. HT indicates hemorrhagic transformation; IV, intravenous; mRS, modified Rankin disability scale; NIHSS, National Institutes of Health Stroke Scale; PS, propensity score; tPA, tissue plasminogen activator.

*For the symptomatic HT and 3-month mortality, exact logistic regression analyses were performed.

†Adjusted for age, sex, baseline NIHSS score, and onset to arrival time.

‡Adjusted for age, NIHSS, and total cholesterol.

Table 6. Odds Ratios (OR) for Function Outcomes at 3 Months by Standard Care With IV Thrombolysis Compared Without IV Thrombolysis in Patients Who Presented With Small Vessel Occlusion

	mRS 0 to 1 at 3 Months		
	OR	95% CI	*P* Value
Crude analysis	0.57	0.25 to 1.29	0.18
Multivariable analysis*	0.97	0.31 to 3.03	0.95
PS matching†	0.95	0.22 to 4.21	0.95
PS matching with additional adjustments‡	1.16	0.28 to 4.87	0.84

OR for IV thrombolysis. BUN indicates blood urea nitrogen; CT, computerized tomography; DM, diabetes mellitus; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin disability scale; NIHSS, National Institutes of Health Stroke Scale; PS, propensity score; SBP, systolic blood pressure; SYSO, symptomatic stenosis or occlusion of the major cerebral arteries.

*Adjusted for age, sex, baseline NIHSS score, onset to arrival time, hypertension, DM, history of stroke, antiplatelet, SBP, fasting glucose, BUN, total cholesterol, CT, CT angiography, MRI, and SYSO.

†PS-matched sample included 15 pairs.

‡Adjusted for age, sex, baseline NIHSS score, and onset to arrival time.

number of outcome events, we reduced the number of covariates for adjustment in the second analysis, which might lead to inadequate adjustment since significant baseline imbalances existed between the patients treated with IVT and without IVT. Further research with a larger sample size is needed to address the optimal clinical criteria for identifying candidates for IVT among mild stroke patients.

The symptomatic HT frequencies in mild stroke patients treated with IVT in observational studies have been reported in a range of 0% to 3.7%, which are quite lower than those reported in acute stroke trials in general.[13,15,32] Since baseline NIHSS is closely related to the occurrence of symptomatic HT in patients treated with IVT,[33–36] the symptomatic HT rate is expected to be low in mild stroke patients. In the present study, symptomatic HT occurred in 8 patients (4.1%) in the IVT group and 6 patients (0.5%) in the standard care without IVT group. We used the European Cooperative Acute Stroke Study 3 criteria to define symptomatic HT. In the IVT arm of the European Cooperative Acute Stroke Study 3 trial, symptomatic HT occurred in 2.4%.[2] The symptomatic HT frequency of 4.1% in the IVT group of our study is higher than expected but may reflect a higher baseline risk among Korean patients. Such high risk of HT would partially mitigate the effectiveness of IVT in Korean patients with mild ischemic stroke symptoms.

Compared with previous reports on mild ischemic stroke, the proportion of subtypes of ischemic stroke differed in that the LAA subtype was the most common subtype and UDE or other determined etiology were less common (Table 7).[8,11,12,26] As we described in the Methods section, we applied modified Trial of Org 10172 in Acute Stroke Treatment criteria to facilitate the diagnosis of LAA presenting with branch atheromatous diseases or infarctions of brain regions outside of lacunar stroke. In addition to these modifications, active application of new imaging techniques such as high-resolution wall imaging in some of our centers might contribute to the increase of LAA and the decrease of UDE.

Our study has several limitations. The data originated from an observational stroke registry database allowing us to study effectiveness but not efficacy, which would require a clinical trial setting. Inevitable imbalances in baseline characteristics between the patients treated with IVT and without IVT occurred as expected, and the possibility of unmeasured or residual confounding cannot be excluded. However, we attempted to minimize the influence of baseline imbalances and measured confounding by PS analysis with additional adjustments and inclusion of variables, which were not usually used in analytic models for the efficacy of IVT but that could affect the treatment decision, such as diagnostic neuroimaging modalities, symptomatic steno-occlusion of major cerebral arteries, and prior medication use.[11,12,26] Nonetheless, our PS model included only total NIHSS scores. We were unable to match the patients using each NIHSS item since the patients showed variable combinations of NIHSS items and the number of patients receiving thrombolytic therapy was relatively small. Since the NIHSS is not a disability score and individual items could produce quite different magnitudes of disability, the PS model based on only total NIHSS scores could be misleading. Of the 194 patients treated with IVT, 50 patients (25.8%) received a tPA dose of 0.6 mg/kg. Although previous studies from Japan showed that the efficacy and

Table 7. Subtype of Ischemic Stroke in Mild Stroke Patients

Stroke Subtype	Nedeltchev et al[8] (n=123)	Urra et al[12] (n=203)	Greisenegger et al[26](n=890)	Logallo et al[11] (n=1784)	Choi et al (n=1384)
LAA	26 (21.1)	23 (11.4)	188 (21.1)	247 (13.8)	460 (33.2)
SVO	28 (22.8)	43 (21.4)	44 (9.9)	250 (14.0)	273 (19.7)
CE	30 (24.4)	58 (28.4)	240 (27.0)	462 (25.9)	282 (20.3)
UDE or ODE	39 (31.7)	79 (38.7)	374 (42.0)	825 (46.2)	369 (26.7)

Values are number of patients (%). CE indicates cardioembolism; LAA, large-artery atherosclerosis; ODE, stroke of other determined etiologies; SVO, small-vessel occlusion; UDE, stroke of undetermined etiology.

safety of the low-dose IV tPA is comparable to that of the standard dose,[27,28,37] use of the low-dose tPA might weaken the effectiveness of IVT in mild stroke patients. Since we included patients according to their initial NIHSS scores, neurologic worsening after initial evaluation as a cause for receiving IVT despite initially mild symptoms was not considered in the analysis. Therefore, adjustment based on initial NIHSS scores only could be misleading. In addition, we must take into account that we had a relatively small number of symptomatic HTs and mortalities in this registry database. The proportions of patients receiving IVT in the 12 participating centers ranged from 0% to 35%, and this could affect the outcome as a confounder in the analysis. However, at the same time, this difference in the IVT rate among the hospitals provided an opportunity to evaluate the effectiveness of IVT by providing comparable cases and controls for conducting this comparative-effectiveness research study. Lastly, our study is based on data from 12 university hospitals or regional stroke centers in Korea, and these results may not be generalizable to other practice settings or other patient populations.

In conclusion, this comparative-effectiveness analysis based on a prospective multicenter stroke registry lends exploratory support to the administration of IVT for mild ischemic stroke. However, one must keep in mind that such administration may carry an increased risk of symptomatic HT. Our observational findings must be validated in a clinical trial setting such as the Potential for rt-PA to Improve Strokes with Mild Symptoms (PRISMS) trial, which will launch soon and is scheduled to be completed in 2018 [http://clinicaltrials.gov/show/NCT02072226].[38]

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Disclosures

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