Safety and Effectiveness of Intravenous Thrombolysis for Acute Ischemic Stroke Outside the Coverage of National Health Insurance in Taiwan

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Abstract-

Purpose: Only a small percentage of ischemic stroke patients were treated with intravenous thrombolysis in Taiwan, partly because of the narrow reimbursement criteria of the National Health Insurance (NHI). We aimed to assess the safety and effectiveness of intravenous thrombolysis not covered by the NHI.

Methods: This is a retrospective analysis of register data from four hospitals. All patients who received intravenous tissue plasminogen activator and fulfilled the American Heart Association/American Stroke Association (AHA/ASA) thrombolysis guidelines between January 2007 and June 2012 were distinguished into two groups: those in accordance (reimbursement group) and those not in accordance (non-reimbursement group) with the NHI reimbursement criteria. Primary outcome was symptomatic intracerebral hemorrhage (SICH). Secondary outcomes were dramatic improvement in the National Institutes of Health Stroke Scale (NIHSS) score at discharge, good functional outcome (modified Rankin Scale ≤2) at discharge, and all-cause in-hospital mortality.

Results: In 569 guideline-eligible patients, 177 (31%) were treated without reimbursement. The reasons for exclusion from reimbursement included age >80 (n=42), baseline NIHSS <6 (n=29), baseline NIHSS >25 (n=15), thrombolysis beyond 3 hours (n=49), prior stroke with diabetes (n=28), use of oral anticoagulant (n=2), and more than one contraindication (n=12). Overall, we observed no differences between the reimbursement and non-reimbursement groups in the rate of SICH (7% versus 6%), dramatic improvement (36% versus 36%), good functional outcome (39% versus 37%), and in-hospital mortality (8% versus 6%)

Conclusion: In stroke patients treated with intravenous thrombolysis according to the AHA/ASA guidelines, the outcomes were comparable between the reimbursement and non-reimbursement groups.

Key Words: Acute ischemic stroke, National Health Insurance, outcome, thrombolysis

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INTRODUCTION

Thrombolytic therapy with intravenous tissue plasminogen activator (tPA) is currently the major approved treatment for acute ischemic stroke (AIS). Even with the burgeoning endovascular therapy, intravenous thrombolysis remains the first choice for treatment of AIS in most stroke centers. The question of whether all the contraindications in the drug label are appropriate has been attracting attention[1,2], partly because only a limited number of patients are free of any contraindications[3]. Of note, studies in European countries have shown that off-label thrombolysis has comparable safety and effectiveness as on-label use[4-6].

Taiwan launched a single-payer universal National Health Insurance (NHI) program in 1995. The NHI program started to reimburse tPA for AIS in 2004. The NHI reimbursement criteria have almost exactly coincided with the regulatory drug license, which was dated in November 2002. Most of the regulations were adapted or modified from the initial National Institute of Neurological Disorders and Stroke (NINDS) clinical trial published in 1995[7], and remained unchanged for nearly 20 years. According to a study based on the NHI claims database, the utilization rate of thrombolytic therapy increased from 0.03% in 2003 to 1.51% in 2010[8]. Even after a nationwide quality improvement campaign in 2010 to 2011, only a minority of patients with AIS (4.6%) were treated with intravenous tPA in the participating hospitals of the campaign[9]. One of the reasons for this low treatment rate might be the restrictive criteria for intravenous tPA adopted by the NHI[10]. In contrast, based on the evidence from the latest studies in two decades, the American Heart Association /American Stroke Association (AHA/ASA) have advised more relaxed criteria for intravenous thrombolysis for AIS in the 2013 guidelines[11].

In Taiwan, the outcomes in patients treated with intravenous tPA outside the NHI reimbursement criteria have not been well studied, neither is the clinical practice in light of the discrepancy between the new AHA/ASA guidelines and the NHI reimbursement criteria. Therefore, using register data from four hospitals, we aimed to compare the safety and effectiveness of intravenous tPA treatment between guideline-eligible patients with and without conformity to all the NHI criteria for reimbursement of intravenous tPA. The potential impact of the NHI reimbursement criteria on clinical practice was also addressed.

METHODS

Through a joint initiative of 4 Taiwan stroke centers (National Cheng Kung University Hospital, Chi-Mei Medical Center, Chia-Yi Christian Hospital, and Landseed Hospital), data were pooled from the individual hospital-based stroke registries, which followed the operation of the nationwide Taiwan Stroke Registry and prospectively registered all stroke patients presenting within 10 days of onset[12]. Stroke severity at baseline and at discharge was evaluated using the National Institutes of Health Stroke Scale (NIHSS). All thrombolyzed patients underwent computed tomography or magnetic resonance imaging between 24 and 36 hours after thrombolysis and additional scans in case of clinical deterioration. Functional status was assessed with the modified Rankin Scale (mRS) at discharge. The study protocol was approved by the individual Institutional Review Board of each participating hospital.

We identified all stroke patients treated with intravenous tPA between January 2007 and June 2012. Patients who were eligible for tPA treatment following the AHA/ASA guidelines[11] were included in this study. We categorized patients into the reimbursement group and the non-reimbursement group according to whether they met the NHI eligibility criteria for reimbursement of tPA (Table 1)[13]. For example, patients with any of the following conditions could not be reimbursed for thrombolytic treatment: aged <18 or >80 years, time to treatment >3 hours, minor stroke (NIHSS <6), severe stroke (NIHSS >25), seizure at onset of stroke, intracranial tumors, major surgery or serious trauma within 10 days, oral anticoagulation with an international normalized ratio >1.3, history of diabetes mellitus and prior stroke, and history of gastrointestinal ulcer within 3 months. We acknowledge that although minor or rapidly improving stroke has been a license contraindication to thrombolysis in Taiwan, the NHI advises specifically against reimbursement for thrombolysis in patients with baseline NIHSS <6 during the study period.

The primary outcome was occurrence of symptomatic

intracerebral hemorrhage (SICH). Following the NINDS trial[7], we defined SICH as any neurological worsening (NIHSS ≥1) within 36 hours of tPA administration that is attributed to intracerebral hemorrhage verified by computed tomography or magnetic resonance imaging. The secondary outcomes included dramatic improvement at discharge (a reduction of ≥10 points from admission NIHSS score, or NIHSS score ≤1[14]), all-cause in-hospital mortality, and good functional outcome (mRS ≤2) at discharge.

Continuous variables were summarized as mean (standard deviation) or median (interquartile range), and categorical variables as counts and percentages. Chi-square tests or Fisher's exact tests were used to compare categorical variables; t-tests or Mann-Whitney U tests were used for continuous variables where appropriate. Using the reimbursement group as the reference, we further performed univariate analysis in various subgroups of patients. In subgroups of ≥15 patients, we also conducted multivariate logistic regression analysis using the reimbursement group as the reference and adjusting for potential confounders to examine the association of each distinct contraindication with outcomes. Depending on the number of events, we chose those more appropriate covariates for adjustment without using any variable selection process. The goodness-of-fit of models was assessed using the Hosmer-Lemeshow test. We considered P values of <0.05 (two-tailed) statistically significant. All analyses were performed with Stata 11 (StataCorp, College Station, Texas).

RESULTS

A total of 624 consecutive patients were identified from the stroke registries (National Cheng Kung University Hospital, n=246; Chi-Mei Medical Center, n=192; Chia-Yi Christian Hospital, n=143; Landseed Hospital, n=43). Among them, 55 patients were excluded because they were not eligible for intravenous thrombolysis according to the AHA/ASA guidelines. Of the remaining 569 patients, 177(31%) were in the non-reimbursement group. Patients in the non-reimbursement group were older, more likely to have diabetes mellitus or prior stroke, and thrombolyzed later than those in the reimbursement group. Lower dose appeared more common

Table 1. Reimbursement criteria of the National Health Insurance.

Inclusion criteria
Clinically suspected acute ischemic stroke, within 3 hours of symptom onset
No evidence of intracranial hemorrhage on brain CT
Age between 18 and 80 years
Exclusion criteria
Time of symptom onset > 3 hours or uncertain before treatment begins
Minor (NIHSS <6) or rapidly improving stroke
Severe stroke (NIHSS >25 or hypodensity >1/3 MCA territory on CT)
Seizure at onset of stroke
Serious head trauma or prior stroke within 3 months
History of prior stroke combined with diabetes mellitus
Treated with heparin within 48 hours with an elevated aPTT
Platelet count <100,000/mm^3
Active internal bleeding
Intracranial tumor
Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg or a need for aggressive treatment to reduce blood pressure to within these limits
Blood glucose <50 or >400 mg/dl
Known bleeding diathesis within 6 months
Current use of oral anticoagulants (INR >1.3)
History of central nervous system lesion (tumor, aneurysm, intracranial or spine surgery)
History of subarachnoid hemorrhage or intracranial hemorrhage
History of severe and poorly controlled hypertension
Major surgery or serious trauma within 10 days
Prolonged or traumatic cardiopulmonary resuscitation (>2 min), delivery or recent (<10 days) vessel puncture at a non-compressible site
Hepatic failure, liver cirrhosis, portal hypertension or acute hepatitis
Hemorrhagic retinopathy
Bacterial endocarditis, pericarditis
Acute pancreatitis
History of gastrointestinal ulcer within 3 months
Aneurysm, arteriovenous malformation
Tumor with bleeding tendency
Allergy to tissue plasminogen activator
Others (uremia with hemodialysis, severe congestive heart failure, poor general condition)

aPTT, activated partial thromboplastin time; CT, computed tomography; INR, international normalized ratio; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Characteristics of the study patients.

	Reimbursement group (n = 392)	Non-reimbursement group (n = 177)	*P* value
Demographics			
Age, mean (SD), y	65 (11)	71 (13)	<0.001
Female, n (%)	142 (36)	65 (37)	0.984
Medical history, n (%)			
Hypertension	289 (74)	139 (79)	0.261
Diabetes mellitus	104 (27)	75 (42)	<0.001
Hyperlipidemia	222 (57)	106 (60)	0.525
Atrial fibrillation	117 (30)	46 (26)	0.400
Prior stroke	49 (13)	52 (29)	<0.001
Current smoking	136 (35)	53 (30)	0.309
Antiplatelets	86 (22)	44 (25)	0.509
Warfarin	4 (1)	5 (3)	0.145a
Clinical data			
Baseline NIHSS score, median (IQR)	13 (9-18)	13 (7-21)	0.230
Systolic blood pressure, mean (SD), mm Hg	160 (30)	161 (31)	0.924
Glucose, mean (SD), mg/dL	150 (61)	157 (67)	0.183
OTT, median (IQR), min	125 (97-155)	151 (115-185)	<0.001
Dosage of tPA, mean (SD), mg/kg	0.85 (0.13)	0.82 (0.13)	0.025

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OTT, onset to treatment time; SD, standard deviation; tPA, tissue plasminogen activator.

[a] Fisher's exact test.

among patients who did not meet the NIH reimbursement criteria (Table 2).

In the non-reimbursement group, 165 patients (93%) had one contraindication and 12 (7%) had more than one contraindication. For those with a single contraindication, the most prevalent causes were treatment time >3 hours, age >80 years, minor stroke (NIHSS <6), and prior history of stroke and diabetes mellitus (Table 3). Thrombolytic treatment resulted in similar (unadjusted) rate of SICH between the two groups, 7% for the reimbursement group versus 6% for the non-reimbursement group. Overall, both groups had similar outcomes with respect to dramatic improvement at discharge (36% versus 36%), good functional outcome at discharge (39% versus 37%), and in-hospital mortality (8% versus 6%) (Table 3).

Compared to those in the reimbursement group, the subgroup of patients aged >80 years were less likely to have an mRS ≤2 at discharge (10% versus 39%); otherwise both groups had similar outcomes. The subgroup of patients with baseline NIHSS <6 were more likely to have dramatic improvement at discharge (55% versus 36%), and good functional outcome at discharge (76% versus 39%). Patients with baseline NIHSS score >25 had a higher rate of SICH (27% versus 7%) and in-hospital mortality (33% versus 8%). However, we found no significant difference in outcomes of dramatic improvement at discharge or good functional outcome at discharge between this subgroup of patients and the reimbursement group. Patients treated within 3 to 4.5 hours of symptom onset, and those with a combination of prior stroke and diabetes mellitus had similar outcomes as compared with those in the reimbursement group (Table 3).

The adjusted odds ratios (adjusted for age, NIHSS score, and glucose level in assessing SICH; adjusted for age, NIHSS score, onset to treatment time, diabetes mellitus, prior stroke, atrial fibrillation, and glucose level while assessing dramatic improvement or good functional outcome at discharge; adjusted for age, NIHSS score, and atrial fibrillation in assessing in-hospital mortality) are shown in Table 4. The results of multivariate regression models did not materially change the observed univariate associations. The P values of the Hosmer-Lemeshow

Table 3. Clinical outcomes between the reimbursement and non-reimbursement groups.

	SICH	Dramatic improvement at discharge	mRS 0–2 at discharge	In-hospital mortality
Reimbursement group (n=392)	28 (7)	143 (36)	154 (39)	30 (8)
Non-reimbursement group (n=177)	11 (6)	63 (36)	65 (37)	10 (6)
Age >80 (n=42)	2 (5)	10 (24)	4 (10)*	3 (7)
NIHSS <6 (n=29)	1 (3)	16 (55)*	22 (76)*	0 (0)
NIHSS >25 (n=15)	4 (27)*	5 (33)	2 (13)	5 (33)*
OTT 3–4.5 h (n=49)	1 (2)	17 (35)	19 (39)	1 (2)
Prior stroke and DM (n=28)	2 (7)	9 (32)	13 (46)	1 (4)
OAC and INR 1.31–1.70 (n=2)	0 (0)	1 (50)	1 (50)	0 (0)
>1 contraindication (n=12)	1 (8)	5 (42)	4 (33)	0 (0)

Data are number (percentage).

DM, diabetes mellitus; INR, international normalized ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; OTT, onset to treatment time; SICH, symptomatic intracerebral hemorrhage.

*P <0.05 as compared with the reimbursement group by Fisher's exact test.

Table 4. Adjusted odds ratio for various outcomes comparing patients with a distinct contraindication with those in the reimbursement group.

	SICH[a]	Dramatic improvement at discharge[b]	mRS 0-2 at discharge[b]	In-hospital mortality[c]
Age >80	0.50	0.48	0.17*	0.61
	(0.11-2.24)	(0.23-1.03)	(0.06-0.53)	(0.17-2.21)
NIHSS <6	0.51	2.38*	4.79*	-
	(0.07-3.89)	(1.09-5.23)	(1.96-11.71)	
NIHSS >25	4.33*	0.95	0.25	5.48*
	(1.26-14.86)	(0.31-2.91)	(0.05-1.13)	(1.70-17.64)
OTT 3–4.5 h	0.28	0.98	0.87	0.27
	(0.04-2.14)	(0.52-1.85)	(0.46-1.68)	(0.03-2.09)
Prior stroke and DM	0.89	0.84	1.70	0.42
	(0.20-4.01)	(0.37-1.95)	(0.72-3.97)	(0.05-3.28)

Data are odds ratio (95% confidence interval) using the reimbursement group as the reference.

DM, diabetes mellitus; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OTT, onset to treatment time; SICH, symptomatic intracerebral hemorrhage.

[a] Models adjusted for age, NIHSS score, and glucose level. P values of the Hosmer-Lemeshow statistics were 0.290, 0.096, 0.783, 0.476, and 0.524.

[b] Models adjusted for age, NIHSS score, onset to treatment time (minute), DM, prior stroke, atrial fibrillation, and glucose level. P values of the Hosmer-Lemeshow statistics were 0.296, 0.680, 0.076, 0.500, and 0.330.

[c] Models adjusted for age, NIHSS score, onset to treatment time (minute), DM, prior stroke, atrial. P values of the Hosmer-Lemeshow statistics were 0.921, 0.955, 0.980, 0.118, and 0.500.

The prespecified covariate was not included in the multivariable logistic regression model if it was the studied contraindication. fibrillation, and glucose level

[d] Models adjusted for age, NIHSS score, and atrial fibrillation.

P values of the Hosmer-Lemeshow statistics were 0.724, 0.240, 0.568, and 0.417.

* *P* <0.05.

goodness-of-fit for all models were greater than 0.05, indicating adequate model fit.

DISCUSSION

Our study highlights two important observations. First, the outcomes of patients in the non-reimbursement group were similar to those of patients in the reimbursement group. This implies that thrombolysis beyond the NHI reimbursement criteria in Taiwanese patients might be safe and effective if the patients meet the AHA/ASA guidelines. Second, approximate one third of the study patients (177 out of 569) would have lost the opportunity to benefit from thrombolytic therapy if the treating physicians had adhered strictly to the NHI reimbursement criteria.

Age >80 years is a common contraindication in patients treated within 3 hours. Our study indicated that these patients had similar outcomes as compared with the reimbursement group, except good functional outcome at discharge. Underlying comorbidities and poor premorbid functional level in the elderly patients might contribute to worse functional outcome at discharge. Nowadays, more and more data suggest that age alone should not be a contraindication for thrombolysis[15-18]. The third International Stroke Trial (IST-3), which studied the benefits and harms of intravenous thrombolysis within 6 hours, justified extending the treatment to patients aged older than 80 years[19]. Among a subgroup of participants of the IST-3, follow-up data showed that the proportional effect of intravenous thrombolysis on survival up to 3 years was not modified by whether age was older than 80 or not[20]. Furthermore, Taiwanese octogenarians and nonagenarians who received intravenous tPA had similar risks of SICH and 3-month mortality as compared to their counterparts in the Western countries[21].

As the incidence and prevalence of stroke increase with age, about 30% of AIS patients might be older than 80 years[22]. Of all the thrombolyzed patients in our study, only 7.4% (42/569) were aged more than 80 years. Although other coexisting contraindications might be more prevalent in the elderly population, we cannot exclude the possibility that clinicians tended to avoid thrombolytic therapy in otherwise eligible elderly patients, and thus might have divested their opportunity to benefit from the treatment. Even though aged patients might have poorer outcomes, higher mortality, and more SICH than younger counterparts, intravenous thrombolysis within 3 hours is still beneficial and is now equally recommended by the AHA/ASA for patients <80 and >80 years of age[23].

Patients with minor stroke were generally excluded from intravenous thrombolysis because they were conventionally considered “too good to be treated” and thus might not worth exposing to the risk associated with thrombolysis. As shown in our study, although thrombolysis in patients with a low baseline NIHSS score resulted in higher percentages of dramatic improvement and good functional outcome than that in patients in the reimbursement group, it still carried a small risk of SICH (Table 3). However, several studies have revealed that 20–27% of patients who did not receive intravenous tPA because of mild or improving symptoms turned out to have an unfavorable outcome[24-26]. In an international Delphi study, specialists in the field of thrombolysis reached a consensus on treating patients with an NIHSS score of as low as 2 to 3[27]. In addition, NIHSS ≤3 might more closely suit the definition of minor stroke because it predicted a favorable 3-month functional outcome in 90% of patients[28]. Therefore, it might not be justified to withhold thrombolytic therapy in patients with baseline NIHSS <6. As an encouraging step forward, the NHI has revised its reimbursement policy to cover patients with baseline NIHSS ≥4 in 2015[29].

On the other hand, we found that major stroke with baseline NIHSS >25 was associated with higher risks of SICH and in-hospital mortality after intravenous thrombolysis. Stroke of such severity is expected to result in poor functional outcome and even mortality by natural course. Therefore, it is not surprising to find a similar higher in-hospital mortality in patients with severe stroke undergoing thrombolysis in other populations[5,17]. Nevertheless, our data also indicated that patients with severe stroke could be thrombolyzed effectively as measured by the extent of improvement in NIHSS score at discharge. Similar results have been shown in other studies. A pooled analysis of tPA trials suggested that thrombolytic therapy might still benefit patients with severe stroke[30]. The IST-3 demonstrated an increasing adjusted odds ratio (thrombolyzed patients versus control) for a good outcome with rising NIHSS[19]. These findings arguably supported intravenous thrombolysis

in patients with severe AIS. Also, according to the data of the aforementioned follow-up study of the IST-3, the proportional effect of intravenous thrombolysis on survival up to 3 years was not modified by stroke severity[20]. A recent meta-analysis of individual patient data from randomized trials suggested the benefits of IV tPA were irrespective of stroke severity[18].

In our study, safety and outcomes profiles were comparable between patients thrombolyzed within 3 hours and those treated between 3 and 4.5 hours. In addition to the positive results of the ECASS III trial[31], data from a registry study showed that intravenous tPA could be administered safely between 3 and 4.5 hours from stroke onset and could improve outcomes[32]. A meta-analysis also indicated that although earlier treatment was associated with better outcomes, intravenous thrombolysis significantly improved the overall odds of a good stroke outcome when delivered within 4.5 hours[18]. Currently, a majority of European Union countries and Japan approved the extended 4.5-hour time window[33,34]. Because the US Food and Drug Administration has not yet approved the extended time window, the AHA/ASA guidelines recommend additional exclusion criteria in selecting patients for intravenous thrombolysis beyond the 3-hour time window[11].

Our data, in conjunction with other studies[4,5], demonstrated that intravenous thrombolysis in patients with a combination of prior stroke and diabetes mellitus was safe and effective. As a vascular risk factor for stroke, diabetes mellitus is more prevalent in Asian patients[35]. In addition, stroke recurrence is frequent. Therefore, it is not uncommon for AIS patients to have concomitant diabetes and prior stroke. A study found that about 8% of 5,817 patients with AIS had both diabetes mellitus and prior stroke, and the functional outcomes were better among patients with diabetes or prior stroke who were thrombolyzed than those not receiving thrombolysis[36]. The authors of that study concluded that withholding thrombolysis from otherwise eligible patients might not be reasonable.

Of note, the administered dose of tPA was significantly lower in the non-reimbursement group. It is possible that clinicians used a lower dose to avoid the risk of hemorrhagic complications when they treated patients outside the NHI eligibility criteria. In particular, a significant trend of increasing SICH with increasing doses of intravenous tPA was reported in Chinese patients aged 71 to 80 years[37]. Moreover, the low-dose intravenous tPA (0.6 mg/kg up to a maximum of 50 mg) could save out-of-pocket expense paid by the patients, and might have become an attractive low-cost option in Asia[38]. Although a large randomized controlled trial did not prove the noninferiority of low-dose tPA to standard-dose tPA in predominantly Asian patients regarding the clinical efficacy, it showed a significantly lower risk of SICH with low-dose tPA[39].

While the rate of intravenous thrombolysis among AIS admissions has become a quality indicator for hospital accreditation in Taiwan, the current NHI reimbursement policy does not provide adequate support for either patients or healthcare providers[40]. Our study revealed that up to 31% of thrombolyzed patients who met the AHA/ASA guidelines would have been excluded from treatment if the NHI reimbursement criteria had been followed. A previous study suggested that thrombolysis candidates could be doubled (from 14% to 33%) if the restricted reimbursement criteria of the NHI program is relaxed[10]. Furthermore, whether thrombolytic therapy is reimbursed by the NHI has deeply impacted the clinical decision making, among others. Up to 93% of patients who were tPA eligible according to the NHI reimbursement criteria consented to thrombolytic therapy, while only 17% of patients who were not eligible for reimbursement by the NHI but were otherwise indicated for treatment according to the AHA/ASA guidelines underwent thrombolytic therapy[10].

The current exclusion criteria for intravenous thrombolysis of various stroke guidelines are constantly challenged by the latest scientific findings. Furthermore, some of these exclusion criteria are controversial and are considered to be relative contraindications by many stroke experts[41]. Clinicians should access and apply up-to-date management guidelines to their acute ischemic stroke treatment decisions to improve outcomes after stroke[23]. Therefore, in order to expand the safe and judicious use of thrombolytic therapy for AIS and save outcast patients, it is time to consider amending the decade-old NHI reimbursement criteria.

Our study has several limitations. First, selection bias probably existed for the non-reimbursement group

because clinicians tended to select these patients with extra caution. Second, the quality of post-thrombolysis care was likely to be different between the reimbursement and non-reimbursement groups. For example, attending physicians might have been more alert to neurological deterioration in patients of the non-reimbursement group. Third, the limited patient number in each type of contraindication precluded a more complete adjustment in the multivariate analysis. Fourth, data on patients who had the same contraindications but did not receive tPA were not available for comparison.

In conclusion, our study shows that the current NHI criteria for reimbursing intravenous tPA in AIS might be too narrow. Adopting more relaxed criteria to expand the coverage of intravenous thrombolysis could benefit more stroke patients and improve the quality of acute stroke care in Taiwan.

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