Original Article

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The Impact of Gender on Mortality and Symptomatic Intracerebral Hemorrhage in Acute Ischemic Stroke Patients After Intravenous Recombinant Tissue Plasminogen Activator (rt-PA)

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Abstract:

Objective: The characteristics and risk factors of stroke differ between men and women. Women have a lower mortality but a higher disability rate after a stroke, as well as a higher rate of response to intravenous recombinant tissue plasminogen activator (rt-PA). However, the data regarding gender and outcomes after rt-PA in Asian populations is limited. Hence, this study aimed to make a comparison between men and women regarding mortality and symptomatic intracerebral hemorrhage (S-ICH) after rt-PA.

Material and Methods: This was a retrospective cohort study conducted in a specialized stroke unit at a 1000-bed university hospital in Thailand. Adult patients, who were eligible for rt-PA, were recruited from the Stroke Fast Track Registry between 2015-2019. The clinical data and radiological results were collected and analyzed.

Results: There was a total of 278 patients,138 of whom were men (49.6%). The men had a lower average age (63 vs. 68 years, p-value<0.001), had higher creatinine levels and higher diastolic blood pressure than the women (1.22±0.93 vs. 0.97±0.84 mg/dl, and 90±15 vs. 86±18 mmHg, all p-values<0.001). The mortality and S-ICH rates were comparable (2.3% vs. 5%, and 8.0% vs. 11.4%, respectively, all p-values>0.05). Having had a history of anti-platelet therapy was a strong risk factor for S-ICH in men (OR 6.43, 95% CI 1.39–29.69); whereas, age was significantly associated with mortality in women (OR 1.13, 95% CI 1.03–1.24).

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Conclusion: Men and women had similar rates of mortality and S-ICH after rt-PA.

Keywords: Asian, complications, gender differences, stroke, thrombolysis

Introduction

Stroke is the fifth leading cause of death in the United States; affecting nearly 800,000 patients a year[1,2]. For patients with disabling acute ischemic stroke (AIS), strategies to improve neurological outcomes include thrombolytic therapy within 4.5 hours and/or mechanical thrombectomy within 24 hours after the onset of symptoms in selected cases[1].

The 2019 guidelines for the early management of patients with AIS recommend intravenous (IV) or intra-arterial administration of thrombolytic drugs; as recanalization has a high success rate[3]. It was also recommended that the care of stroke patients should involve a multidisciplinary team in the pre-hospital, in-hospital and rehabilitation phases[4].

The impact of gender on the clinical presentation and outcomes of stroke was first studied in the US in 2008[5]. The study found that women had experienced more stroke events due to their longer life expectancy[5]. Furthermore, women, who experienced strokes, had had a higher prevalence of hypertension, atrial fibrillation and pre-stroke disability; however, they exhibited a lower prevalence of heart disease, peripheral vascular disease, smoking and alcohol use[5]. The Biobank cohort study, in the United Kingdom, also reported that hypertension, smoking and a lower socio-economic status had been risk factors for strokes in women[6]. However, compared to men, women, who suffered from ischemic strokes, had been less likely to receive IV thrombotic therapy, and thus exhibited poorer functional outcomes after strokes[5]. Furthermore, women were found to have had a lower quality of life with more episodes of depression after strokes than men[5]. The Australian Stroke Clinical Registry also reported a higher stroke mortality rate in hypertensive women than in men[7].

A cohort study in rural China showed that the incidence of stroke was higher in men than in women[8]. Meanwhile, the body mass index (BMI), systolic blood pressure (SBP), total cholesterol, triglycerides, low-density lipoprotein (LDL), rate of antihypertensive drug use; and a rate of low physical activity was found to be higher in women[8]. In a study in rural Taiwan, the in-hospital mortality rate of stroke victims did not differ significantly with respect to gender; although the functional outcomes at discharge and at six months after a stroke had been poorer in women than in men[9].

Although, the prevalence of stroke in Thailand is high (1,880 per 100,000 population during 2004-2006)[10], there is little information regarding the impact that gender has on mortality, and on the functional outcomes in the Thai population or that of Southeast Asia as a whole. Consequently, this study was aimed at determining the differential association of gender with mortality and S-ICH after thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA).

Material and Methods

Study design and population

This was a retrospective cohort study, which examined the data registry from the specialized stroke unit of Khon Kaen University's Srinagarind Hospital (Khon Kaen, Thailand). All patients who were eligible for rt-PA according to the hospital's activated Stroke Fast Track System; from January 2015 to December 2019, were enrolled. Moreover,

all of the enrolled patients had been treated in accordance with the standard stroke guidelines[11]. Each patient's National Institute of Health Stroke Scale (NIHSS) score[12] was recorded, and a computed tomography (CT) brain scan was performed prior to receiving rt-PA and then between 22 to 36 hours after.

Those patients with incomplete neurological monitoring data within the first 24 hours and those having received other invasive interventions for ischemic stroke; such as endovascular revascularization or surgery, were excluded from the study.

The Khon Kaen University Ethics Committee for Human Research approved this study and waived the requirement for informed consent (HE631202).

Objective

The aim of this study was to determine the differential impact of gender on mortality and S-ICH.

Data collection

Medical records were registered in the hospital object (H.O.) database, while hand-written clinical record forms were scanned and collected from the Praxis web server. Brain computed tomography (CT) images and results were collected from the hospital's Picture Archiving and Communication System (PACS). The patients' vital signs and laboratory results were retrieved from the H.O. database. Demographic data, weight, height, social history, underlying diseases, medications, onset time, time to rt-PA; baseline neurological status and the neurological outcome scores were gathered from the Praxis web server.

Outcome measures and variables of interest

1. Symptomatic intracerebral hemorrhage (S-ICH)

Symptomatic intracranial hemorrhage or S-ICH after rt-PA was identified according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SIST-MOST) criteria[13], and from the definitions presented in the European Cooperative Acute Stroke Study 3 (ECASS-3)[14].

2. Neurological status and functional outcomes

In addition to the NIHSS score, the Modified Ranking Score (mRS)[15], the Glasgow Coma Scale score (GCS)[16], and the Barthel index[17]; prior to and after rt-PA administration, were collected from the medical records.

3. Mortality

The mortality rate was calculated based on the all causes of in-hospital death, as recorded in the medical records.

Statistical analysis

Categorical variables were presented as numbers and percentages, while the continuous variables were summarized as mean±S.D. or median (interquartile range [IQR]): as appropriate. The chi-square test of independence was used to compare the categorical variables between men and women, while the independent sample t-test was used to compare continuous variables. Univariate analysis was performed to examine the relationship between the outcome (mortality or S-ICH) and age, gender, SBP, DBP and the other conventional cardiovascular risk factors (hypertension, diabetes mellitus (DM), smoking history, laboratory parameters and medications). The association of gender with each outcome was presented as an unadjusted odds ratio (95% confidence interval [CI]). The statistical significance was defined as a p-value<0.05. SPSS version 26 and STATA version 10.1 were used for these analyses.

Results

The demographic data and the differences between men and women

There were 278 ischemic stroke patients who had been eligible for rt-PA and for whom the complete data was

available during the study period. Of these, 138 (49.6%) were men. The mean was 65.4±13.0 years, and mean weight was 59.3±13.2 kilograms (kg). The men had a lower mean age (62.8±11.8 vs. 68.1±13.5 years) and a higher mean weight (63.7±13.2 vs. 54.9±11.7 kg) than the women (all p-value<0.001). The men also had lower LDL (115.5 vs. 123 mg/dl), but higher levels of creatinine and HbA1C (1.00 vs. 0.83 mg/dL and 5.9% vs. 5.7%, respectively) compared to the women. However, these differences were not found to be statistically significant. The numbers of men and women with hypertension, DM, arterial disease and AF had been similar (all p-values>0.05). However, there was a higher rate of men being current smokers (37% vs. 2.1%, p-value<0.001; Table 1)

Clinical presentation, treatment, and outcomes of ischemic stroke in men and women

The MCA territory was the most common ischemic stroke location in both men and women (50.7% and 58.6%, respectively). Small vessel strokes were the second most common diagnosis (26.8% in men and 25% in women), which was followed by no obvious pathology (15.9% in men and 13.6% in women). Cerebellar strokes were rare, occurring in around 2% of both men and women. There were no women who had experienced a brain stem stroke, compared to 1.5% of men. There were five patients who had experienced a stroke in more than one vascular territory; four of whom were men (Table 1).

There had been no differences in neurological status prior to rt-PA therapy. Median GCS, NIHSS, Barthel index, and mRS had been 14 (11-15) vs. 15 (11-15), 10 (6-15) vs. 10 (7-16), 30 (10-50) vs. 27.5 (5-47.5), and 4 (4-4) vs. 4 (4-5) in men and women, respectively (all p-value> 0.05). After rt-PA administration, neurological status had improved, but did not differ according to gender. Median GCS, NIHSS, Barthel index and mRS post-administration had been 14 (13-15) vs. 14 (12-15), 5 (2-12) vs. 5 (1.5-12), 67.5 (15-100) vs. 60 (10-90), and 3 (1-4) vs. 4 (1-5), respectively (all p-values>0.05; Table 1).

Time from onset to rt-PA had not been found to differ according to gender (3.1±1.9 hours in men vs. 3.1±1.6 hours in women, p-value=0.722). Neither had the rate of IV nicardipine administration differed between pre-rt-PA and post-rt-PA (Table 1).

There were 27 patients having experienced S-ICH (9.7%); from this 10 had died (3.6%). However, the rates of S-ICH (8% vs. 11.4%, p-value=0.330) and mortality (2.2% vs. 5%, p-value=0.206) had not differed according to gender. However, women had a longer median hospital stay than men (3 [2-4] days vs. 2 [2-4] days, p-value=0.011).

Comparison between the S-ICH and the non-S-ICH group

There were 27 patients having developed S-ICH after rt-PA (9.7%). The S-ICH group had been slightly older than the non-S-ICH group (69.8 vs. 65.0 years, p-value =0.065); however, the weight and gender distribution had been similar. Interestingly, the S-ICH group consisted of a higher percentage of patients with AF (51.8% vs. 21.5%, p-value<0.001), while those patients having other concomitant diseases; including hypertension and DM, had been similar.

The S-ICH group had shown a significantly lower initial SBP (142 mmHg vs. 152 mmHg, p-value =0.042) and DBP (79 mmHg vs. 87 mmHg, p-value=0.014) before rt-PA administration in addition to higher SBP variation profiles (SD, 16 mmHg vs. 13 mmHg; CV, 10 mmHg vs. 9 mmHg; SV, 20 mmHg vs. 17 mmHg; all p-values<0.05; median [IQR]). Although, the DBP variation profiles (SD, CV, and SV) had been higher in the S-ICH group, this difference was not determined to be significant (Table 1).

Table 1 The baseline characteristics of acute ischemic stroke patients categorized by gender

Characteristics	All patients (N=278)	Women (n=140)	Men (n=138)	p-value
Age, years (mean±S.D.)	65.4±13.0	68.1±13.5	62.8±11.8	<0.001
Weight, kg (mean±S.D.)	59.3±13.2	54.9±11.7	63.7±13.2	<0.001
Active smoker, n (%)	54 (19.4)	3 (2.1)	51 (37.0)	<0.001
Initial blood pressure (mean±S.D.)				
SBP, mmHg	153±28	154±30	153±26	0.903
DBP, mmHg	88±17	86±18	90±15	0.044
Laboratory results (median (IQR))				
LDL, mg/dl	119.5 (93–146)	123 (92.5–145.5)	115.5 (93–146)	0.545
Creatinine, mg/dl	0.92 (0.76–1.14)	0.83 (0.68–1.01)	1.00 (0.89–1.20)	<0.001
HbA1c, %	5.8 (5.3–6.6)	5.7 (5.3–6.6)	5.9 (5.3–6.7)	0.950
Hematocrit, %	38.1 (34.3–41.6)	35.7 (32.9–38.9)	40.45 (37.1–43.2)	<0.001
INR	1.03 (0.98–1.10)	1.02 (0.98–1.10)	1.04 (1.00–1.11)	0.210
Underlying diseases, n (%)				
Hypertension	122 (43.9)	65 (46.4)	57 (41.3)	0.389
Diabetes mellitus	60 (21.6)	34 (24.3)	26 (18.8)	0.270
Previous stroke	17 (6.1)	11 (7.9)	6 (4.4)	0.222
Arterial disease	20 (7.2)	9 (6.4)	11 (8.0)	0.619
AF	131 (47.1)	65 (46.4)	66 (47.8)	0.815
Prior medications, n (%)				
Anti-hypertensive	78 (28.1)	39 (27.9)	39 (28.3)	0.940
Anti-platelet	25 (9.0)	15 (10.7)	10 (7.3)	0.312
Anti-coagulant	13 (4.7)	8 (5.7)	5 (3.6)	0.409
Times to r-TPA, hr (mean±S.D.)	3.1±1.8	3.1±1.6	3.1±1.9	0.722
Areas of infarction, n (%)				
No obvious pathology	41 (14.8)	19 (13.6)	22 (15.9)	0.474
MCA territory	152 (54.7)	82 (58.6)	70 (50.7)	
Small vessel	72 (25.9)	35 (25.0)	37 (26.8)	
Stroke in more than one vascular territory	5 (1.8)	1 (0.7)	4 (2.9)	
Cerebellar	6 (2.2)	3 (2.1)	3 (2.2)	
Brain stem	2 (0.7)	0	2 (1.5)	
Neurological status: Pre-rt-PA (median (IQR))				
GCS	15 (11–15)	15 (11–15)	14 (11–15)	0.413
NIHSS	10 (6– 6)	10 (7–16)	10 (6–15)	0.632
Barthel index	30 (5–50)	27.5 (5–47.5)	30 (10–50)	0.165
mRS	4 (4–5)	4 (4–5)	4 (4–4)	0.051
Neurological status: Post-rt-PA (median (IQR))				
GCS	14 (12–15)	14 (12–15)	14 (13–15)	0.897
NIHSS	5 (2–12)	5 (1.5–12)	5 (2–12)	0.899
Barthel index	65 (10–95)	60 (10–90)	67.5 (15–100)	0.124
mRS	3 (1–4)	4 (1–5)	3 (1–4)	0.142
IV Nicardipine, n (%)				
Pre rt-PA	32 (11.5)	17 (12.1)	15 (10.9)	0.739
Post rt-PA	54 (19.4)	25 (17.9)	29 (21.0)	0.509
Outcomes				
S-ICH, n (%)	27 (9.7)	16 (11.4)	11 (8.0)	0.330
LOS, day median (IQR)	3 (2–4)	3 (2–4)	2 (2–4)	0.011
Dead, n (%)	10 (3.6)	7 (5.0)	3 (2.2)	0.206

AF=atrial fibrillation, DBP=diastolic blood pressure, GCS=Glasgow Coma Scale, HbA1c=Hemoglobin A1c, ICH=intracranial hemorrhage, INR=international normalized ratio, IQR=interquartile range, LDL=low-density lipoprotein, LOS=length of stay, MCA=middle cerebral artery, mRS=modified Rankin Scale, NIHSS=National Institutes of Health Stroke Scale, rt-PA=recombinant tissue plasminogen activator, SBP=systolic blood pressure, S.D.=standard deviation, S-ICH=symptomatic intracranial hemorrhage

Association between gender and outcomes after rt-PA

When using males as the reference group, females had not been associated with S-ICH (OR 1.49, 95% CI 0.67–3.34, p-value=0.333), with death (OR 2.37, 95% CI 0.60–9.35, p-value=0.219) nor with the composite outcome (OR 1.85 95% CI 0.87–3.93, p-value=0.108; Table 2). It was also found that being female had not impacted the mRS at discharge (mRS 1–2, OR 1.60, 95% CI 0.74–3.46, p-value=0.233 and mRS 3–6, OR 1.52, 95% CI 0.94–2.46, p-value=0.091; Table 2).

Determinants of S-ICH and mortality

In the total population of this study, anti-platelet therapy prior to rt-PA was the only independent factor that had been associated with S-ICH (OR 5.31; 95% CI: 1.35–20.97), and after adjustment for age, gender, DM, hypertension, smoking history, BMI, Cr and LDL, only age had been significantly associated with death (OR 1.10, 95% CI: 1.02–1.17 Table 3).

Table 2 The outcomes after intravenous thrombolysis and women's odds ratio for each outcome (men = reference group)

Outcomes	Women (n=140) n (%)	Men (n=138) n (%)	OR (95% CI)	p-value
mRS 1-2 at discharge	128 (51.6)	120 (48.4)	1.60 (0.74–3.46)	0.233
mRS 3-6 at discharge	92 (54.4)	77 (45.6)	1.52 (0.94–2.46)	0.091
S-ICH	16 (59.3)	11 (40.7)	1.49 (0.67–3.34)	0.333
Dead	7 (70.0)	3 (30.0)	2.37 (0.60–9.35)	0.219
Composite outcome	21 (63.6)	12 (36.4)	1.85 (0.87–3.93)	0.108

mRS=modified Rankin Scale, S-ICH=symptomatic intracranial hemorrhage

Table 3 The determinants of symptomatic intracerebral hemorrhage (S-ICH) among women and men

Characteristics	Women (n=140)		Men (n=138)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, per 1 year	1.02 (0.98–1.06)	0.379	1.05 (0.99–1.11)	0.110
SBP, per 1 mmHg	0.99 (0.97–1.01)	0.187	0.98 (0.96–1.01)	0.209
DBP, per 1 mmHg	0.97 (0.94–1.01)	0.092	0.96 (0.92–1.00)	0.067
Diabetes mellitus, yes=1, no=0	2.06 (0.69–6.16)	0.197	1.70 (0.42–6.89)	0.460
Hypertension, yes=1, no=0	2.09 (0.72–6.11)	0.178	1.79 (0.52–6.17)	0.358
Creatinine, per 1 mg/dl	0.64 (0.15–2.78)	0.551	0.93 (0.43–2.01)	0.846
Anti-platelet, yes=1, no=0	3.42 (0.94–12.44)	0.061	6.43 (1.39–29.69)	0.017
Anti-coagulant, yes=1, no=0	2.81 (0.52–15.28)	0.232	3.08 (0.31–30.19)	0.335
Anti-hypertensive drug, yes=1, no=0	1.65 (0.56–4.91)	0.364	2.28 (0.65–7.96)	0.196
Atrial fibrillation, yes=1, no=0	0.89 (0.31–2.53)	0.820	3.17 (0.80–12.51)	0.099
Time to rt-PA per 1 minute	0.99 (0.70–1.39)	0.951	0.53 (0.28–1.00)	0.050

DBP=diastolic blood pressure, rt-PA=recombinant tissue plasminogen activator, SBP=systolic blood pressure

Table 4 The determinants of in-hospital mortality among women and men

Characteristics	Women (n=140)		Men (n=138)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, per 1 year	1.13 (1.03–1.24)	0.013	1.04 (0.93–1.15)	0.498
SBP, per 1 mmHg	1.00 (0.98–1.03)	0.951	1.00 (0.96–1.05)	0.964
DBP, per 1 mmHg	1.03 (0.99–1.07)	0.095	1.02 (0.95–1.10)	0.583
HT, yes=1, no=0	0.44 (0.08–2.37)	0.343	0.71 (0.06–7.97)	0.778
Creatinine, per 1 mg/dl	0.77 (0.13–4.48)	0.771	0.08 (0.01–18.83)	0.369
Atrial fibrillation, yes=1, no=0	7.53 (0.88–64.25)	0.065	0.54 (0.05–6.08)	0.617
Time to r-TPA per 1 minute	0.60 (0.28–1.29)	0.192	0.40 (0.11–1.48)	0.170

DBP=diastolic blood pressure, rt-PA=recombinant tissue plasminogen activator, SBP=systolic blood pressure

However, after categorizing patients according to gender, it was found that anti-platelet therapy had been associated with S-ICH in men (OR 6.43, 95% CI 1.39–29.69), but not in women (OR 3.42, 95% CI 0.94–12.44). Interestingly, age had been associated with in-hospital mortality in women (OR 1.13, 95% CI 1.03–1.24), but not in men (OR 1.04, 95% CI 0.93–1.15 Table 4).

Discussion

A global study of stroke burden and its risk factors was conducted by region between 1990-2019. The study reported that stroke remained the second-highest cause of death as well as the third-highest cause of combined death and disability[18]. In addition, the annual number of strokes and deaths due to stroke increased substantially over the period of the study[18]. Countries having been categorized as low-income by the World Bank, showed the highest stroke-related mortality rates and disability-adjusted life-years (DALY)[18]. Moreover, during that period it was found that high body mass index (BMI) was the fastest-growing risk factor for stroke[18].

Successful treatment of ischemic stroke using thrombolytic therapy was first reported in 1958[19]. However, over the following decades its use was abandoned after conducted trials reported unacceptable rates of intracranial hemorrhage post-therapy[3]. It was later revived due to the development of a new drug that could be used to successfully treat acute myocardial ischemia. In addition, a meta-analysis of several pilot studies examining thrombolytic therapy for ischemic strokes showed that its benefits outweighed its risks[19].

In 1996, a panel of the American Heart Association (AHA) Stroke Council recommended using thrombolytic therapy to treat acute ischemic stroke[3]. At that time, both intravenous administration and intra-arterial administration of thrombolytic drugs were considered to be equally effective, given that the success rate of recanalization varied from 21.0 to 93.0%[19]. Since that time, there have been various studies conducted on the following: 1) when thrombolytic drugs should be administered, 2) who should receive the drugs, and 3) how to make certain that 'the golden period of treatment' is not missed.

A 2008 study conducted in the US was the first to examine differences in stroke epidemiology based on gender[5]. It found that women with strokes had a higher prevalence of hypertension, AF and pre-stroke disability[5]. Conversely, this study found that women and men had similar rates of hypertension, DM and AF. However, in this

study it was revealed that women had a lower prevalence of smoking compared to men: this was consistent with the findings of the previous study[5].

In the US study, women had been less likely to receive IV thrombolytic therapy, which indicated that they had tended to have poorer functional outcomes after stroke[5]. The women and men in our database were equally likely to be treated with rt-PA, and the outcomes after stroke were similar for both mortality and neurological outcomes (e.g., S-ICH). However, in this study any data focusing on the quality of life (QOL) or on mental status was not collected. The results of a more recent cohort study, which was conducted in the United Kingdom; with a larger population and a longer follow-up (9 years), indicated that the incidences of all types of strokes in women were lower than in men, despite their being several risk factors strongly associated with the female gender[6]. The risk factors in women for all types of stroke were; hypertension, smoking and low socio-economic status. Interestingly, DM was found to be a risk factor for ischemic stroke in women but not in men[6].

Although stroke epidemiology has been shown to differ between Asian and Caucasian patients, compared to studies conducted in Western countries, epidemiologic studies of stroke in Asian populations have had sample sizes that were relatively small.

A cohort study of 5,097 hypertensive patients in rural China showed that the incidences of all types of strokes had been higher in men than in women[8]. Similarly, stroke was found to be more prevalent in men than women in the Thai population (aged 45-84 years)[10]. However, the average age of stroke onset in Chinese men was higher than in women, which differed from the results of this study. The LDL in women was higher than in men[8], which was consistent with the results of this study.

In rural Taiwan, another study was conducted to examine in-hospital mortality and the functional outcomes of 4,278 patients admitted to a stroke unit. Similar to our results, the in-hospital mortality rate had not differed significantly between men and women. However, the functional outcomes at discharge and at six months after stroke in Taiwanese women had been poorer than in men. Meanwhile, this study found a similar rate of S-ICH in men and women. Hypertension was an independent risk factor for poor functional outcomes in Taiwanese women, as was AF for in-hospital mortality[9]. This study found that anti-platelet therapy had been associated with S-ICH in men but not in women; while age had been associated with in-hospital mortality in women but not in men.

For this study, there were some limitations. Firstly, the data was collected from a single center in rural Thailand. Although the treatment of ischemic stroke has been standardized, the population may, in terms of biology and cultural background, differ from others. Therefore, care should be taken when extrapolating the results. Secondly, a differential association between long-term outcomes and gender was not revealed. Finally, as mentioned above, QOL and mental status were not evaluated.

Conclusion

It was found that men and women had similar rates of mortality and S-ICH after rt-PA. Therefore, gender should not be a factor when making the decision to initiate rt-PA treatment. Although advanced age and history of anti-platelet therapy are not absolute contraindications for rt-PA treatment, such patients should be closely monitored and observed for neurological complications.

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Conflict of interest

All authors have no conflicts of interest to be declared.

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