

Comparison of outcome of patients with acute minor ischaemic stroke treated with intravenous t-PA, DAPT or aspirin

Peng Wang,¹ Mengyuan Zhou ,² Yuesong Pan ,³ Xia Meng,³ Xingquan Zhao,² Liping Liu ,² Hao Li,³ Yongjun Wang ,² Zhimin Wang,⁴ Yilong Wang,² on behalf of the CHANCE investigators

To cite: Wang P, Zhou M, Pan Y, *et al.* Comparison of outcome of patients with acute minor ischaemic stroke treated with intravenous t-PA, DAPT or aspirin. *Stroke & Vascular Neurology* 2021;**6**: e000319. doi:10.1136/svn-2019-000319

PW and MZ contributed equally.

Received 3 January 2020
Revised 6 August 2020
Accepted 30 August 2020
Published Online First
19 October 2020



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¹Neurology Department, Zhejiang Provincial People's Hospital, Hangzhou, China

²Neurology Department, Beijing Tiantan Hospital, Beijing, China

³China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Beijing, China

⁴Neurology Department, The First people's Hospital of Taizhou, Taizhou, China

Correspondence to
Professor Yilong Wang;
yilong528@gmail.com

ABSTRACT

Background Whether to treat minor stroke with intravenous tissue plasminogen activator (t-PA) treatment or antiplatelet therapy is a dilemma. Our study aimed to explore whether intravenous t-PA treatment, dual antiplatelet therapy (DAPT) and aspirin have different efficacies on outcomes in patients with minor stroke.

Methods A post hoc analysis of patients with acute minor stroke treated with intravenous t-PA within 4.5 hours from a nationwide multicentric electronic medical record and patients with acute minor stroke treated with DAPT and aspirin from the Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack Database. Minor stroke was defined by a score of 0–3 on the National Institutes of Health Stroke Scale at randomisation. Favourable functional outcome (defined as modified Rankin Scale (mRS) score of 0–1 or 0–2 at 3 months).

Results Compared with those treated with intravenous t-PA, no significant association with 3-month favourable functional outcome (defined as mRS score of 0–1) was found neither in patients treated with aspirin (87.8% vs 89.4%; OR, 0.83; 95% CI, 0.46 to 1.50; $p=0.53$) nor those treated with DAPT (87.4% vs 89.4%; OR, 0.84; 95% CI, 0.46 to 1.52; $p=0.56$). Similar results were observed for the favourable functional outcome defined as mRS score of 0–2 at 3 months.

Conclusions In our study, no significant advantage of intravenous t-PA over DAPT or aspirin was found. Due to insufficient sample size, our study is probably unable to draw such a conclusion that that intravenous t-PA was superior or non-superior to DAPT.

INTRODUCTION

There are approximately 3 million new-onset strokes occurring each year based on recent estimates of stroke incidence, of which about 30% are minor stroke.¹ However, only 44% of those suffered acute minor stroke or transient ischaemic attack (TIA) were treated within 3 hours of onset.² Approximately 10%–20% patients experience a subsequent stroke in 3 months, and half of them suffer it within 2 days after the initial stroke.^{3 4} However, the strategy to the high recurrence is limited. The main strategy is dual antiplatelet therapy (DAPT). The Clopidogrel

with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) study and the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) study quantified that the addition of clopidogrel to aspirin reduced the risk of recurrent stroke by 32.0% and 27%, respectively.^{5 6} Yet, those patients are still at risk of long-term poor outcomes.

Intravenous tissue plasminogen activator (t-PA) as one of the most valid managements for acute ischaemic stroke, is controversial for patients with minor stroke.⁷ Insufficient evidence of intravenous thrombolysis in patients with minor stroke is one of the main reasons. Most of the randomised controlled trials considered minor stroke as an exclusion criterion.^{8–10} Lack of recognition or action on symptoms is another reason, delaying seeking medical attention and missing the optimal time window of thrombolysis.^{2 11} A previous study indicated that 30% of patients with minor stroke not receiving intravenous t-PA treatment may develop poor outcomes.¹² Several studies showed that patients with minor stroke might benefit from the intravenous t-PA treatment,^{13 14} especially in those with stroke subtype of large-artery atherosclerosis.¹⁵ The 2018 guidelines for acute ischaemic stroke recently recommended that patients with minor but disabling stroke symptoms within 3 hours could be treated with intravenous t-PA, and intravenous t-PA might also be reasonable for those with minor stroke in the 3–4.5 window.¹⁶

Up to now, evidence on the necessity of intravenous t-PA treatment for patients with acute minor stroke is lacking and ambiguous. Thus, the present study aimed to explore whether intravenous t-PA treatment, DAPT and aspirin have different efficacies on outcomes in patients with minor stroke compared with aspirin.

METHODS

Study population

Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China)¹⁷ and Third China National Stroke Registry (CNSR-III)¹⁸ with sharing unified data collection standards and core data are two independent registries involved in National Stroke consortium of China National Quality Control Center for stroke. Researchers and clinical research coordinators of each centre are responsible for involving patients who meet criteria and sign informed consent prospectively and consecutively. The independent third-party clinical research organisation (GiantCRO) is responsible for data recording and tracing in electronic medical record. Researchers of China National Clinical Research Center for Neurological Diseases are independent and responsible for data audit. Patients with minor stroke treated with intravenous t-PA (Actilyse, Boehringer Ingelheim, Germany) within 4.5 hours after symptom onset were acquired from the TIMS-China and CNSR-III during May 2009 to December 2017. The inclusion criteria were (1) aged from 18 to 80; (2) received a clinical diagnosis of stroke; (3) had a cerebral CT or MRI scan ruling out haemorrhage, major ischaemic infarction, or other non-ischaemic diseases; (4) had no contraindication for thrombolysis therapy. Patients with cardioembolic aetiology were excluded. Well-trained neurologists documented the baseline characteristics of participants including demographics, medical history, CT or MRI scan of brain, intravenous thrombolysis information and 3-month follow-up information from EMR system. The protocol was approved by the ethics committee of every centre that participated. Informed consent of all patients or their representatives were obtained.

Patients receiving DAPT and aspirin were obtained from the CHANCE study database.⁵ The CHANCE study was a national randomised, double-blind, placebo-controlled clinical trial conducted from October 2009 to July 2012 in China.⁵ A full description of the design, rationale and methodology was issued previously.¹⁹ A total of 5170 patients with minor stroke or high risk TIA were involved. Patients with minor stroke received DAPT and aspirin within 4.5 hours were included in the present study. All the participants or their legal proxies provided written informed consent. The protocol was approved by the ethics committee at each study centre.

Minor stroke was defined by a score of 3 or less at the time of randomisation on the National Institutes of Health Stroke Scale (NIHSS). We extracted the following variables: demographics (including age, sex, weight), medical history (including smoking, independence (modified Rankin Scale, mRS score of 0–1) prior to stroke, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidaemia, previous stroke and TIA), stroke severity (measured by NIHSS), stroke onset to treatment time, etc.

Patient and public involvement

Participants were not involved in setting of the research agenda. The results of the study will be disseminated to study participants through access to the published article once published in the journal.

Outcome assessments

Both databases collected the information of mRS score at 3 months. We defined favourable functional outcome as mRS score of 0–1 at 90 days or mRS score of 0–2 at 90 days. The primary safety outcomes of intravenous t-PA treated patients were symptomatic intracranial haemorrhage (sICH) rate at 24–36 hours based on European Co-operative Acute Stroke Study-II (ECASS II) study,²⁰ and mortality at 90 days. The definition of sICH was any type of intracranial bleeding accounting for clinical deterioration (eg, drowsiness, increase of hemiparesis) or a decrease of ≥ 4 NIHSS score.²¹ The primary safety outcome in the CHANCE trial was a moderate-to-severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries definition.

Statistical

Categorical variables were presented as percentages and continuous variables as median (Q1–Q3) or mean \pm SD. Pearson's χ^2 or Fisher's exact tests were applied to categorical variables, and t-test or Mann-Whitney tests for continuous variables.

ORs with 95% CIs for the favourable functional outcome were calculated by multivariable logistic regression model in total patients in the aspirin group as the reference. The model was adjusted for sex, age, smoking, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, previous stroke, previous TIA, blood glucose, blood pressure, weight, NIHSS score and mRS prior to stroke. A propensity score indicating the predicted probability of receiving aspirin and DAPT was conducted in the sensitivity of analysis. The propensity for the aspirin and DAPT was determined regardless of the outcome using a non-parsimonious multivariable logistic regression model. All baseline variables listed in table 1 were included to calculate the propensity score, and was then calculated from the logistic equation for each patient. The propensity score was then included along with the comparison variable (intravenous t-PA, DAPT and aspirin) in multivariable analyses of outcome to produce an adjusted OR with 95% CI.

All P values were 2-sided, with P values < 0.05 considered significant. All analyses were performed with SAS software V.9.4.

RESULTS

A total of 385 intravenous t-PA treated patients with minor stroke were included from the nationwide multi-centric electronic medical record, and 215 DAPT treated patients and 230 aspirin treated patients with minor stroke

Table 1 Baseline variables of patients

Variables	Aspirin (n=230)	DAPT (n=215)	Intravenous t-PA (n=385)	P value
Age (years), median (IQR)	62.2 (54.8–72.2)	63.8 (55.2–71.2)	61.0 (54.0–69.0)	0.10
Sex, male (%)	149 (64.8)	149 (69.3)	257 (66.8)	0.60
Medical history (%)				
Smoking	97 (42.2)	87 (40.5)	157 (40.8)	0.92
Independence (mRS 0–1) prior to stroke	177 (77.0)	175 (81.4)	334 (86.8)	0.007
Atrial fibrillation	11 (4.8)	12 (5.6)	17 (4.4)	0.81
Hypertension	137 (57.8)	135 (62.8)	252 (65.5)	0.34
Diabetes mellitus	43 (18.7)	52 (24.2)	77 (20.0)	0.32
Hyperlipidaemia	21 (9.1)	22 (10.2)	35 (9.1)	0.89
*Previous stroke	51 (22.2)	42 (19.5)	65 (16.9)	0.26
Previous TIA	4 (1.7)	7 (3.3)	14 (3.6)	0.40
Median blood glucose (mmol/L)	5.3 (4.9–6.1)	5.7 (4.9–6.9)	5.6 (4.9–7.0)	0.02
Systolic blood pressure (mm Hg)	150±23.1	151.5±21.3	152.7±20.4	0.16
Diastolic blood pressure (mm Hg)	88.9±13.3	88.5±12.2	87.5±12.4	0.35
Weight (kg)	67.9±9.7	70.1±9.8	68.9±11.5	0.07
Median NIHSS score (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.97
Median stroke onset to treatment time (IQR) (hours)	3.5 (2.6–4.0)	3.5 (2.5–4.0)	2.9 (2.2–3.6)	<0.001

Data were presented as median (IQR) for continuous and ordinal variables, and number of patients/total number from whom data were available (%) for categorical variables.

*The previous stroke of patients in the CHANCE study was ischaemic stroke, while it was ischaemic and haemorrhagic stroke in the intravenous t-PA group.

CHANCE, Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack; DAPT, dual antiplatelet therapy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; t-PA, tissue plasminogen activator.

were obtained from the CHANCE study. All of them had complete baseline information (table 1).

Baseline characteristics of patients in three groups were shown in table 1. The median age of intravenous t-PA treated patients, DAPT treated patients and aspirin treated patients was 61.0 years, 63.8 years and 62.2 years, respectively (table 1). Two hundred and fifty-seven patients (66.8%) in intravenous t-PA treated group, 149 patients (69.3%) in DAPT group and 149 patients (64.8%) in aspirin group were male. Patients with acute minor stroke received intravenous t-PA treatment and DAPT had higher blood glucose, better independence prior to stroke and took less time from stroke onset to treatment. The other baseline characteristics were well balanced.

Compared with those treated with intravenous t-PA, no significant association with favourable functional outcome (defined as mRS score of 0–1) was found neither in patients treated with aspirin (87.8% vs 89.4%; OR, 0.83; 95% CI, 0.46 to 1.50; $p=0.53$) nor those treated with DAPT (87.4% vs 89.4%; OR, 0.84; 95% CI, 0.46 to 1.52; $p=0.56$) after adjusting potential covariates at 3 months after stroke. Similar results were observed for the favourable functional outcome defined as mRS score of 0–2 at 3 months (aspirin: 92.6% vs 95.0%; OR, 0.65; 95% CI, 0.30 to 1.39, $p=0.26$; DAPT: 92.6% vs 95.0%; OR, 0.67; 95% CI,

0.31 to 1.48, $p=0.33$), and in models adjusted for propensity score (online supplemental table 1).

As shown in table 2, there were two patients died at 3 months both in the aspirin group and intravenous t-PA group (0.9% vs 0.5%; OR, 0.99; 95% CI, 0.10 to 10.46; $p=0.92$) while no patients died in the DAPT group. The primary safety outcomes were shown in table 3. Eight patients developed sICH according to ECASS II definition in the intravenous t-PA group. Two patients developed minor bleeding event in the DAPT group (one of them was gastrointestinal related bleeding). One patient developed serious bleeding event and one patient developed moderate bleeding event in the aspirin group.

DISCUSSION

Our study did not find significant difference in 3-month functional outcome, neither defined as mRS score of 0–1 nor as mRS score of 0–2, among intravenous t-PA, DAPT and aspirin in patients with acute minor stroke. As the sample size was small, this study was insufficient to infer that intravenous t-PA was superior or non-superior to DAPT or aspirin.

The efficacy and safety of DAPT in patients with minor stroke were demonstrated in previous studies. The Fast assessment of stroke and transient ischemic attack to

Table 2 Main safety and functional outcomes of patients

Outcome	Group	n (%)	Unadjusted		Multivariable adjusted*		PS adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
mRS 0–1 at 3 months	Intravenous t-PA	338 (89.4)	Ref		Ref		Ref	
	Aspirin	202 (87.8)	0.85 (0.51 to 1.43)	0.55	0.83 (0.46 to 1.50)	0.53	0.80 (0.46 to 1.41)	0.44
	DAPT	188 (87.4)	0.82 (0.49 to 1.39)	0.47	0.84 (0.46 to 1.52)	0.56	0.84 (0.48 to 1.48)	0.55
mRS 0–2 at 3 months	Intravenous t-PA	359 (95.0)	Ref		Ref		Ref	
	Aspirin	213 (92.6)	0.66 (0.34 to 1.30)	0.23	0.65 (0.30 to 1.39)	0.26	0.58 (0.28 to 1.22)	0.15
	DAPT	199 (92.6)	0.66 (0.33 to 1.31)	0.23	0.67 (0.31 to 1.48)	0.33	0.64 (0.31 to 1.34)	0.23
Mortality at 3 months	Intravenous t-PA	2 (0.5)	Ref		Ref		Ref	
	Aspirin	2 (0.9)	1.68 (0.24 to 12.00)	0.61	0.99 (0.10 to 10.46)	0.92	1.46 (0.17 to 12.95)	0.73
	DAPT	0 (0.0)	–	0.96	–	1.00	–	0.94

*Adjusted for sex, age, smoking, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, previous stroke, previous TIA, blood glucose, blood pressure, weight, NIHSS score and mRS prior to stroke.
DAPT, dual antiplatelet therapy; EMR, electronic medical record; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience; PS, propensity score; TIA, transient ischaemic attack; t-PA, tissue plasminogen activator.

prevent early recurrence (FASTER) study documented that 300 mg loading dose of clopidogrel within 24 hours of symptom onset followed by aspirin 75 mg daily might reduce risk of stroke and not increase the risk of intracranial haemorrhagic.²² Later, the CHANCE trial was well designed and the result showed that the early and short-term combination of clopidogrel and aspirin significantly reduced the risk of recurrent ischaemic stroke compared with aspirin alone in patients with minor stroke.⁵ The POINT study also illuminated that 90-day application of clopidogrel and aspirin to patients with acute minor stroke significantly reduced incidence of ischaemic events.⁶ The two large scale studies provided an effective management for patients with minor stroke. However, in the present study, no statistical significance was found in patients with DAPT compared with those with aspirin in functional outcome. This has mainly resulted from the small sample size.

Table 3 sICH and bleeding events of patients

Outcome	Aspirin, n (%)	DAPT, n (%)	Intravenous t-PA, n (%)
sICH (per ECASS II)			8 (2.1)
Bleeding (GUSTO)			
Serious	1 (0.4)	0 (0.0)	
Moderate	1 (0.4)	0 (0.0)	
Minor	0 (0.0)	2 (0.9)	
Any bleeding	2 (0.9)	1 (0.5)	

DAPT, dual antiplatelet therapy; ECASS II, European Co-operative Acute Stroke Study-II; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; sICH, symptomatic intracranial haemorrhage; t-PA, recombinant tissue plasminogen activator.

Previous analysis showed that 8.2% of patients with minor stroke were still developing stroke at 3 months, and 10.6% at 1 year after DAPT.²³ The intravenous t-PA is one of the most effective treatments for patients with acute ischaemic stroke, while minor stroke remains the relative contraindication.²⁴ CNSR showed that 41.8% of 2514 patients who presented to emergency department within 3 hours after onset did not receive intravenous t-PA treatment mainly due to mild syndrome and quick remission.²⁵ Although the NINDS recombinant t-PA Stroke Study found no significant difference in the beneficial effects of intravenous t-PA in patients with minor stroke compared with those received placebo, there was a trend that minor stroke patients received intravenous t-PA had favourable outcomes.²⁶ A recent subset analysis of the third International Stroke Trail observed that patients with minor stroke (NIHSS ≤ 5) receiving intravenous t-PA treatment achieved more proportion of alive and independent with Oxfordshire Handicap Score of 0–2.¹⁴ And a pooled analysis of nine randomised trials including 666 patients with NIHSS score of 0–4 showed a potential efficacy of intravenous t-PA treatment in minor stroke.²⁷ The Austrian Stroke Unit Registry found that intravenous t-PA treated patients with mild deficit (NIHSS ≤ 5) had a better outcome after 3 months compared with those without intravenous t-PA treatment.¹³ The Potential of rt-PA for Ischemic Strokes With Mild Symptoms (PRISMS) study recently published the results finding no significant difference in 90-day functional outcome between intravenous t-PA and aspirin. However, the number of patients involved was only 313 which was much less than expectation due to the failure to finish recruitment on time, which made the result less credible.²⁸ A previous study showed that 30% of patients with minor stroke received intravenous t-PA treatment had mRS score of 2–6,¹² the

rate shown in the PRISMS study was 19%.²⁸ Both were higher than the rate we obtained—10.6%. In the present study, patients treated with intravenous t-PA were prone to have favourable functional outcome although the difference was not statistically significant. One possible explanation could be that patients with intravenous t-PA had better independence at presentation, which made the extra benefit from intravenous t-PA unapparent. On another hand, minor stroke was differently defined by NIHSS score. In the present study, we predefined minor stroke as NIHSS ≤ 3 according to the NINDS study⁸ and the CHANCE study.⁵ However, NIHSS score cannot accurately reflect the severity of functional impairment, for instance, conscious disturbance, cognitive deficit, vertigo and other neurological symptoms not included in the NIHSS. In addition, NIHSS score was unable to reflect intracranial artery occlusion. Angiography showed that 48% of minor stroke and transient ischaemic attack patients existed extracranial and intracranial artery occlusion or moderate-to-severe stenosis.²⁹ Thus, even patients with minor stroke with NIHSS score of 0–3 are at high risk of poor functional outcomes.

Our study only found a weak trend but not significant difference among intravenous t-PA treatment, DAPT and aspirin in 3-month functional outcome in patients with acute minor stroke. However, intravenous t-PA treatment might be a potential management for some patients with minor stroke, especially for those with early neurological deterioration (END). The prevalence of END was ranging from 10%–40%, leading to poor short-term and long-term outcome.³⁰ Although symptoms of minor stroke were mild and lesions were small, there were still a portion of patients developing END.³¹ The CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke (CATCH) study showed that not only stroke recurrence, also stroke progression contributed to poor outcome of patients with minor stroke. In addition, the latter was independent risk factor for poor prognosis at 90 days.³² The underlying mechanisms included collateralisation failure, thrombus extension, recurrent stroke, cerebral oedema, haemorrhagic transformation, re-occlusion after recanalisation and seizures.³⁰ DAPT might be effective for prevention of END,³³ but recently a study found that DAPT worked in carriers of cytochrome P450 2C19 loss-of-function alleles while not in non-carriers.³⁴ Minor stroke with intracranial artery occlusion was associated with severe END, and intravenous t-PA treatment might lower risk of non-haemorrhagic END.³⁵ Thus, seeking an optimal approach to acute minor stroke requires a comprehensive consideration of individual's condition. A recent study showed that developing a better comprehension of the outcomes of intravenous t-PA treatment in patients with minor stroke would provide tremendous social value.³⁶ It required well designed randomised clinical trials, larger scale studies and real-world researches to further detect the efficacy and safety of intravenous t-PA treatment in patients with minor stroke.

The risk of sICH in minor stroke patients received intravenous t-PA was consistent with that previously shown, which varied from 0% to 3.7%.^{13 37 38} As reported, the incidence of sICH despite the baseline NIHSS score in the TIMS-China registry was 3.1%,¹⁷ and the rate of moderate-to-severe haemorrhage event in the CHANCE study was 0.3%.⁵ In the present analysis, eight patients (2.1%) developed sICH in the intravenous t-PA group. Although the safety outcomes among 3 therapies were incomparable, IV t-PA treatment seemed to not increase the risk of sICH compared to previous studies. For DAPT, the subanalysis of the CHANCE trial showed that short-term DAPT increased the risk of non-intracranial haemorrhagic event in patients with minor stroke (2.3%).³⁹ The POINT study showed 90-day use of clopidogrel and aspirin also increased the risk of major and minor haemorrhage.⁶ In the present study, 2 patients suffered minor bleeding events in the DAPT group, while two patients suffered moderate-to-serious bleeding events in the aspirin group. Due to different standard for safety outcome measurement, it was difficult to compare the safety among intravenous t-PA, DAPT and aspirin.

There are several limitations of our study. First, the small sample size limited power to estimate the effectiveness and safety of intravenous t-PA treatment and DAPT in patients with minor stroke. The power of estimation between intravenous t-PA and aspirin was 9.5%, and the power of estimation between intravenous t-PA and DAPT was 11.7%, which were inadequate to the conclusion. Second, the criteria of safety outcome were not uniform, making it difficult to compare the safety of these strategies. In addition, this study did not conduct centrally neuroimaging judgement for sICH at 24–36 hours, the sICH definition might be varied among centres. Third, the CHANCE study did not record the aetiology type of stroke. A previous study showed that patients with stroke type of large-artery atherosclerosis might benefit more both from intravenous t-PA treatment and DAPT.⁴⁰

CONCLUSION

In the present exploratory comparative analysis, we only found a weak trend but not significant difference among intravenous t-PA treatment, DAPT and aspirin in 3-month functional outcome in patients with acute minor stroke. For the primary safety outcomes, the present study also did not find significant difference. Due to the insufficient sample size and limited power of estimation, our study is probably unable to draw such a conclusion that intravenous t-PA was superior to DAPT or aspirin. Large sample size study is further needed to compare efficacy and safety of t-PA and DAPT in patients with acute minor stroke.

Contributors Conception and design: PW, MZ, YP, YW and ZW; analysis and interpretation of data: PW, MZ, YP and YW. Drafting the article and revising the content: PW and MZ. All authors approved the final version of the manuscript.

Funding This study was supported by grants from National Natural Science Foundation of China (No. 81825007); Beijing Outstanding Young Scientist Program (No. BJJWZYJH01201910025030); the 'Thirteenth-Five' Key Development and

Research Plan by the Ministry of Science and Technology of the People's Republic of China (No. 2017YFC1307900); Beijing Science and Technology Plan by Beijing Municipal Science and Technology Commission (No. D171100003017001); Beijing Excellent Talents Training and Supporting-Top Youth Team by Beijing Municipal Science and Technology Commission (No. 2016000021223TD03); Beijing Talent Project-Class A: Innovation and Development (No. 2018A12).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Ethical Review Committee of Beijing Tiantan Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. No additional data are available.

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ORCID iDs

Mengyuan Zhou <http://orcid.org/0000-0002-2078-0767>

Yuesong Pan <http://orcid.org/0000-0003-3082-6789>

Liping Liu <http://orcid.org/0000-0003-2943-055X>

Yongjun Wang <http://orcid.org/0000-0002-9976-2341>

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Supplementary Material-Table 1: Main Safety and Functional Outcomes of Patients with Propensity Score Matching Model

Outcome	Group	n (%)	PSM	
			OR (95% CI)	P
mRS 0-1 at 3 months	Aspirin	160/182(87.9)	0.77 (0.39-1.50)	0.44
	DAPT	162/181(89.5)	0.90 (0.45-1.79)	0.77
	IV t-PA	161/178(90.4)	ref	
mRS 0-2 at 3 months	Aspirin	168/182(92.3)	0.79 (0.35-1.79)	0.57
	DAPT	169/181(93.4)	0.93 (0.40-2.16)	0.86
	IV t-PA	167/178(93.8)	ref	
Mortality at 3 months	Aspirin	2/182(1.1)	1.00 (0.14-7.18)	1.00
	DAPT	0/181(0.0)	-	0.96
	IV t-PA	2/182(1.1)	ref	

DAPT indicates dual antiplatelet therapy; IV t-PA, recombinant tissue plasminogen activator; OR, odds ratio; CI, confidence intervals; mRS, modified Rankin scale; PSM, propensity score matching.