

# Comparison of multimodal intra-arterial treatment versus intravenous thrombolysis for hypertensive patients with severe large vessel cerebral infarction

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## ABSTRACT

Since intravenous thrombolysis (IVT) is often associated with poor outcomes in hypertensive patients with severe acute cerebral infarction (ACI) due to occlusions of the internal carotid, basilar, or proximal middle cerebral artery, we evaluated whether multimodal intra-arterial treatment (IAT) might improve functional outcomes in this patient population. We retrospectively reviewed the charts of eligible patients who underwent multimodal IAT including intra-arterial thrombolysis, mechanical thrombectomy, balloon and/or stent angioplasty (IAT group) or IVT alone (IVT group). Outcomes included the revascularization rate 24 hours postprocedure, the frequency of survival at 7, 90, and 180 days postonset, and a measure of functional outcomes using the modified Rankin Scale (mRS). The IAT group included 62 patients and the IVT group included 31 patients. Multimodal IAT increased the revascularization rate at 24 hours ( $p<0.001$ ) and the frequency of survival and functional independence ( $mRS \leq 2$ ) at 7 days ( $p<0.001$  and  $p=0.018$ , respectively), 90 days (both  $p<0.001$ ), and 180 days (both  $p<0.001$ ). Independent predictors of longer survival were treatment with multimodal IAT (HR 0.1; 95% CI 0.0 to 0.4;  $p<0.001$ ) and revascularization (HR 0.1; 95% CI 0.0 to 0.4;  $p<0.001$ ), whereas a longer duration from onset to treatment was a risk factor for death (HR 1.4; 95% CI 1.2 to 1.8;  $p<0.001$ ). There was no significant between-group difference for symptomatic hemorrhagic transformation. This study found that for patients with severe hypertensive ACI with large vessel occlusions, multimodal IAT improved the outcomes, including early revascularization, survival, and functional outcome.

## INTRODUCTION

Acute cerebral infarction (ACI), stemming from occlusion of the internal carotid artery (ICA), basilar artery (BA), or the first segment of the middle cerebral artery (MCA) is usually associated with severe neurological deficits and a dismal natural course.<sup>1,2</sup> Intravenous alteplase, the approved therapy for acute ischemic stroke, is less effective among patients with large vessel

## Significance of this study

### What is already known about this subject?

- For acute ischemic stroke, intravenous thrombolytic therapy is less effective in patients with large vessel than small vessel occlusion due to the associated low rate of timely recanalization.
- Intra-arterial treatment (IAT) usually results in a higher rate of recanalization than intravenous thrombolytic administration alone because IAT permits direct contact between the clot and thrombolytics, enhances enzymatic digestion, facilitates mechanical clot disruption and retrieval, and allows stent implantation as needed.
- However, IAT is more complicated than intravenous treatment and requires more time to prepare a patient for the procedure.
- Since the Prolyse in Acute Cerebral Thromboembolism II study was published in 1999, subsequent trials have provided mixed results; thus, the effectiveness of IAT alone in patients with severe acute cerebral infarction (ACI) is still a matter of debate.

### What are the new findings?

- For patients with severe ACI with hypertension and large vessel occlusion, multimodal IAT was associated with improved early revascularization, survival, and functional outcome.
- Multimodal IAT was associated with a significantly increased revascularization rate at 24 hours and improved survival and functional independence at 7, 90, and 180 days.
- Treatment with multimodal IAT and revascularization were independent predictors of longer survival.

than small vessel occlusion due to the associated low rate of timely recanalization.<sup>3</sup> In addition, it cannot be administered more than 4.5 hours after onset of stroke symptoms or in the presence of contraindications such as severe

## Significance of this study

**How might these results change the focus of research or clinical practice?**

- ▶ This retrospective study focused on a particularly high-risk group of patients, with hypertension, severe ACI caused by large vessel occlusion, and a baseline median National Institutes of Health Stroke Scale score of 22.6, which was higher than in recent randomized controlled trials.
- ▶ This study found that multimodal IAT might achieve good results in a relatively high-risk patient population.
- ▶ Future studies should be undertaken to prove these results in a randomized controlled trial.

uncontrolled hypertension, a bleeding diathesis, or intracranial bleeding.<sup>4</sup>

Compared with intravenous thrombolysis (IVT), intra-arterial treatment (IAT) permits direct contact with the clot to enhance enzymatic digestion and to facilitate mechanical clot disruption and retrieval and the performance of stent implantation, if necessary.<sup>5</sup> Consequently, IAT usually results in a higher rate of recanalization than intravenous tissue-type plasminogen activator (t-PA) alone, although it requires more time to prepare a patient for the former than the latter and is more complicated.<sup>6</sup> For these reasons, IAT, which began in the 1980s with the intra-arterial perfusion of streptokinase, was regarded as an important alternative treatment even before randomized controlled trials were conducted.<sup>7</sup> The Prolyse in Acute Cerebral Thromboembolism II study, which looked at the benefit of using IAT plus heparin versus heparin alone in patients with MCA occlusions who reached the hospital within 6 hours of stroke symptoms (too long for IVT therapy), was published in 1999 and was the first positive IAT trial involving patients with angiographically proven evidence of arterial occlusion.<sup>8</sup>

However, future studies were mixed. In 2004, Yoshimura *et al* published the results of a nationwide, prospective registry study, concluding that endovascular treatment significantly improved clinical outcomes in intravenous alteplase-failed and intravenous alteplase-ineligible patients with occlusions of the main trunk of the ICA/MCA/BA.<sup>9</sup> Then, the Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke,<sup>6</sup> MR RESCUE,<sup>10</sup> and the Interventional Management of Stroke (IMS)-III<sup>11</sup> studies, all published in 2013, did not support the use of IAT over IVT.

Recently, a series of completed prospective, multicenter, randomized trials involving patients with ACI have consistently shown clinical benefits for intravenous alteplase plus intra-arterial mechanical thrombectomy.<sup>12–16</sup> However, all of these trials enrolled patients with ACI who had moderate-to-severe neurological deficits in anterior circulation, and the trials compared endovascular thrombectomy in conjunction with IVT versus IVT alone. Patients with contraindications for IVT were excluded. The effectiveness of IAT alone in patients with severe ACI is still a matter of debate.

Hypertension and cardioembolism are the common traditional etiologies of large vessel cerebral infarction.<sup>9</sup> The hypertension in ACI has a more complex pathogenesis:

the major mechanism for hypertension during acute large vessel occlusion is likely due to cerebral autoregulation to achieve higher cerebral perfusion pressure in light of ischemia—so it is a response. Additionally, hypertension can be a chronic risk factor that may be exacerbated during an acute stroke; usually, there are more complex vascular lesions and greater narrowing of culprit vessels in hypertensive strokes than in cardioembolic strokes.<sup>17 18</sup> Patients with cardioembolic stroke, whose strokes are caused by cardiac conditions that produce emboli, are more likely to be candidates for endovascular thrombi retrieval, whereas in patients with hypertensive ACI, especially those with proliferative plaque formation or stenotic lesions in the culprit artery, multimodal IAT, achieved by intra-arterial thrombolysis, mechanical thrombectomy, or both, has more advantages than endovascular thrombectomy alone.

In the present study, we compare the effect of multimodal IAT with IVT alone in hypertensive patients with severe ACI caused by large vessel occlusion to evaluate whether multimodal IAT is safer and more clinically beneficial than IVT with alteplase for these patients.

**METHODS****Study population**

We retrospectively analyzed inpatients treated for ACI at the First Affiliated Hospital of Guangzhou Medical University and Maoming City People's Hospital (affiliated with Nanfang Medical University) between January 2008 and June 2013. Eligible patients included those patients with ACI with: (1) both a baseline modified Rankin Scale (mRS) score of 5 (range 0 (no symptoms) to 6 (death)) and a National Institutes of Health Stroke Scale (NIHSS) score  $\geq 17$ , suggesting severe neurological deficits (range 0–42, with higher scores indicating greater stroke severity); (2) age  $> 18$  years; (3) large vessel occlusions of the trunks of MCA, ICA, or BA, established with CT and CT angiography (CTA) or diffusion-weighted imaging (DWI) and magnetic resonance angiography (MRA); (4) presentation within 6 hours after onset of symptoms in anterior circulation or within 12 hours in posterior circulation; (5) hypertension as defined by the Joint National Committee (JNC) 7<sup>19</sup>; and (6) those who provided consent to receive follow-up phone calls after discharge. Patients with cardiac conditions, such as atrial fibrillation or rheumatic mitral stenosis, or patients with mechanical prosthetic valves that would produce emboli in the heart and patients with persistent systolic blood pressure (SBP)  $> 180$  mm Hg or diastolic blood pressure (DBP)  $> 110$  mm Hg were excluded, as were patients who met such exclusion criteria for intervention for ischemic stroke such as no femoral pulses or very difficult endovascular access that would result in an inability to deliver endovascular therapy.<sup>6</sup> The study protocol was approved by the two institutional ethics committees. Written informed consents for all patients were obtained before the procedures.

The course of treatment with IVT or IAT was based on patient preferences (or the preference of the patient's family within 4.5 hours of onset of symptoms following discussion with the patient's physician). However, they could not receive alteplase therapy if they arrived at the hospital more than 4.5 hours after onset of symptoms. Patients were

**Table 1** Baseline characteristics of the patients

Variable	IAT (n=62)	IVT (n=31)	p Value
Demographic characteristics			
Age, years	66.6±11.2	64.7±11.5	0.464
Male, n (%)	35 (56.5)	16 (51.6)	0.658
Clinical characteristics			
NIHSS score	23.2±4.7	21.4±4.2	0.066
mRS score	5	5	–
Duration to treatment, hours	5.0 (4.0,6.3)	4.0 (3.0,4.5)	<0.001
Median (IQR)			
SBP (mm Hg)	150.6±14.5	152.5±12.4	0.532
DBP (mm Hg)	85.9±9.7	88.6±10.8	0.224
Blood glucose (mmol/L)	7.9±3.1	8.4±3.6	0.571
TC (mmol/L)	5.0±1.6	5.1±1.5	0.853
TG (mmol/L)	1.4±0.8	1.3±0.7	0.354
HDL (mmol/L)	1.2±0.5	1.4±0.4	0.221
LDL (mmol/L)	3.0±1.1	2.9±1.1	0.629
Medical history			
Hypertension	62 (100)	31 (100)	–
Diabetes	21 (33.9)	8 (25.8)	0.429
Hyperlipidemia	21 (33.9)	11 (35.5)	0.877
Smoking	10 (16.1)	6 (19.4)	0.698
Alcohol abuse	12 (19.4)	4 (12.9)	0.437
Previous cerebral infarction	8 (12.9)	8 (25.8)	0.120
Site of occlusion, n (%)			
MCA	21 (33.9)	14 (45.2)	0.457
ICA	13 (21.0)	7 (22.6)	
BA	28 (45.2)	10 (32.3)	

Data are the mean±SD unless otherwise indicated.

An mRS score of 5 was a requirement to be eligible for inclusion in the study. BA, basilar artery; DBP, diastolic blood pressure; IAT, multimodal intra-arterial treatment; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

categorized as IAT directly and underwent intra-arterial thrombolysis, mechanical thrombectomy, or balloon and/or stent angioplasty up to 6 hours after onset of symptoms, if they had ACI involving the anterior circulation, and up to 12 hours after onset of symptoms, if they had ACI involving the posterior circulation.

Baseline clinical parameters, including age, gender, and common clinical risk factors such as hypertension, hyperlipidemia, and diabetes, were identified through medical record review.

### Clinical, laboratory, and radiological investigations

A diagnosis of hypertension was based on the average of the first three consecutive morning blood pressure measurements being >140/90 mm Hg or on medical history. Blood glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) serum levels were extracted from the charts.

All patients received head CT and CTA or head DWI and MRA scans at admission and 24 hours after treatment to look for evidence of recanalization of large intracranial vessels, changes in the brain at the site of the cerebral

infarction, and hemorrhagic transformation, defined as evidence of brain parenchyma blood visible on head CT 24 hours after procedure. Hemorrhagic transformation was classified as symptomatic if the NIHSS score increased four points greater than baseline<sup>20</sup> or asymptomatic, if not. Reperfusion was assessed according to the modified Mori's grade, with grades 0–3 representing increasing degrees of revascularization from none to complete.<sup>21</sup>

### Treatment

Although patients were offered a choice of treatments when appropriate, all received treatment according to established protocols, which were the same in both hospitals. Patients in the IVT group had undergone rapid treatment with intravenous alteplase (0.9 mg/kg dose, 10% bolus, 90% continuously infused within 60 min). Clopidogrel 75 mg or aspirin 100 mg once daily was administered orally to patients without symptomatic hemorrhagic transformation on CT scan 24 hours postprocedure. The patients in the IAT group had received a 300 mg bolus dose of aspirin followed immediately by multimodal IAT. If these patients also received intra-arterial thrombolysis, the alteplase dose was 0.6 mg/kg. After operation, clopidogrel 75 mg or aspirin 100 mg was given to the patients without symptomatic hemorrhagic transformation once per day. Patients undergoing acute stent implantation were treated with both clopidogrel (75 mg) and aspirin (100 mg) postprocedure.

Blood pressure was lowered to two-thirds of preoperative level by nimodipine or urapidil hydrochloride injection once the culprit vessel was revascularised, with treatment continuing for 7–14 days. Blood pressure was managed in all patients in accordance with JNC 7 beginning 2 weeks after procedure.<sup>19</sup>

### Endovascular therapy

All neurointerventional procedures were performed on an angiography machine (Siemens Axiom Artis, Siemens Healthcare, Munich, Germany) under 1% lidocaine local anesthesia plus fentanyl citrate 0.05–0.1 mg intravenous injection. Angiographic revascularization was evaluated using the modified Thrombolysis in Cerebral Infarction (TICI) grade,<sup>22</sup> ranging from 0 to 3, with successful reperfusion defined as grade 2B (perfusion of half or greater of the arterial territory of the affected artery) or 3 (full perfusion). During procedures, the occlusion site was first confirmed by digital subtraction angiography, and patients received immediate intra-arterial contact thrombolysis if within the 4.5-hour window since the onset of symptoms. Afterwards, if the occluded artery did not achieve recanalization, usually within 30–60 min, the Solitaire FR retrievable stent (Covidien) was deployed to retrieve the thrombosis. If more than 4.5 hours had passed since the onset of the ACI, the thrombosis retrieval was performed by Solitaire FR stent directly. If the affected vessel had a residual stenosis ≥70%, balloon angioplasty was performed but had to be completed within 8 and 14 hours of symptom onset in anterior and posterior circulations, respectively. In cases of tandem stenoses of the affected artery or if the site of residual stenosis showed an angle <145°, stent implantation was considered in order to reduce the incidence of reocclusion or to reduce the risk of perforation of the artery posed by balloon dilation alone.

**Table 2** Clinical outcomes of interventional subgroups

	Solitaire retriever (n=23)	Balloon angioplasty (n=18)	Stent angioplasty (n=10)	p Value
Primary outcomes				
24 hours after procedure				
Recanalization on head CTA/MRA, n (%)	20 (87.0)	14 (77.8)	9 (90.0)	0.689*
7 days after onset				
Survival	23 (100)	16 (88.9)	9 (90.0)	0.207*
Other outcomes				
7 days after onset				
mRS 0–2, n (%)	7 (30.4)	2 (11.1)	1 (10.0)	0.329*
NIHSS (n <sub>solitaire</sub> =23, n <sub>balloon</sub> =16, n <sub>stent</sub> =9)	12.2±7.5	15.3±5.7	15.0±7.7	0.336
90 days after onset				
Survival, n (%)	23 (100)	15 (83.3)	9 (90)	0.093*
mRS 0–2, n (%)	16 (69.6)	6 (33.3)	3 (30.0)	0.035*
NIHSS (n <sub>solitaire</sub> =23, n <sub>balloon</sub> =15, n <sub>stent</sub> =9)	6.6±7.0	8.6±7.2	8.7±6.7	0.605
180 days after onset				
Survival, n (%)	23 (100)	14 (77.8)	8 (80.0)	0.035*
mRS 0–2, n (%)	16 (69.6)	7 (38.9)	4 (40)	0.101*
NIHSS (n <sub>solitaire</sub> =23, n <sub>balloon</sub> =14, n <sub>stent</sub> =8)	5.5±7.0	7.4±7.3	7.0±6.7	0.706
Safety outcomes at 7 days after onset, n (%)				
Symptomatic hemorrhagic transformation	0 (0.0)	1 (5.6)	0 (0.0)	0.549*
Asymptomatic hemorrhagic transformation	4 (17.4)	5 (27.8)	2 (20.0)	0.718

\*Using Fisher's exact test.

Data are the mean±SD unless otherwise indicated.

CTA, CT angiography; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

When the affected vascular territory achieved successful reperfusion (TICI 2b or 3) and following repeat angiography in 30 min, the procedure was terminated. Procedures

were also terminated if the affected artery had not revascularized within 8 or 14 hours of symptom onset in the anterior circulation or posterior circulation, respectively.

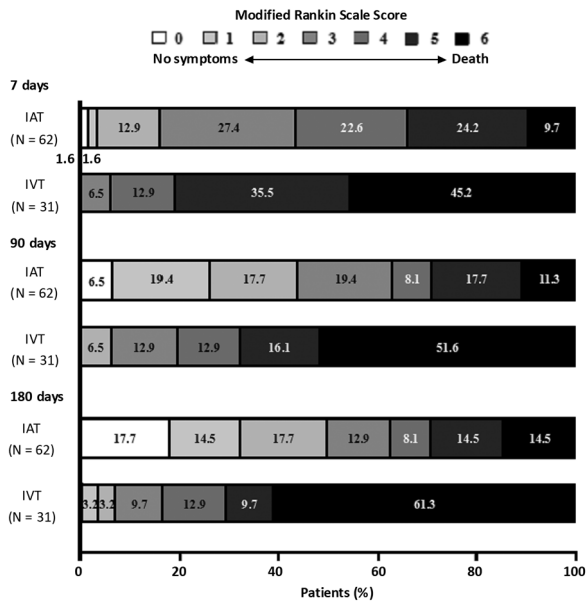
**Table 3** Clinical outcomes

	IAT (n=62)	IVT (n=31)	OR (95% CI)	p Value
Primary outcomes				
24 hours after procedure				
Recanalization on head CTA/MRA, n (%)	48 (77.4)	8 (25.8)	9.9 (3.6 to 26.8)	<0.001
7 days after onset				
Survival, n (%)	56 (90.3)	17 (54.8)	7.7 (2.6 to 23.1)	<0.001
Other outcomes				
7 days after onset				
mRS 0–2, n (%)	10 (16.1)	0 (0)	0.6 (0.5, 0.7)*	0.018
NIHSS (n <sub>IAT</sub> =56, n <sub>IVT</sub> =18), Median (IQR)	12.5 (8.0, 18.0)	17.0 (12.8, 19.3)	N/A	0.087
90 days after onset, n (%)				
Survival	55 (88.7)	15 (48.4)	8.4 (2.9 to 24.1)	<0.001
mRS 0–2	27 (43.5)	2 (6.5)	11.2 (2.5 to 51.1)	<0.001
NIHSS (n <sub>IAT</sub> =55, n <sub>IVT</sub> =15), Median (IQR)	6.0 (3.0, 15.0)	12.0 (6.0, 16.0)	N/A	0.022
180 days after onset, n (%)				
Survival, n (%)	53 (85.5)	12 (38.7)	9.3 (3.4 to 25.6)	<0.001
mRS 0–2, n (%)	31 (50.0)	2 (6.5)	14.5 (3.2 to 66.1)	<0.001
NIHSS (n <sub>IAT</sub> =53, n <sub>IVT</sub> =12)* Median (IQR)	4.0 (1.0, 12.0)	11.5 (6.0, 16.0)	N/A	0.016
Safety outcomes at 7 days after onset, n (%)				
Symptomatic hemorrhagic transformation	3 (4.8)	4 (12.9)	0.3 (0.1 to 1.6)	0.165
Asymptomatic hemorrhagic transformation	12 (19.4)	9 (29.0)	0.6 (0.2 to 1.6)	0.296

\*For cohort group IAT due to 0 patients with mRS 0–2 in IVT group at 7 days after onset.

CTA, CT angiography; IAT, intra-arterial treatment; IVT, intravenous thrombolysis; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.





**Figure 1** Scores on the modified Rankin Scale (mRS) at 7, 90, and 180 days after onset of intra-arterial treatment (IAT) and intravenous thrombolysis (IVT) groups. The mRS scores range from 0 to 6: 0=no symptoms, 1=no significant clinical disability, 2=slight disability (able to take care of own affairs without assistance but unable to fulfill all previous activities), 3=moderate disability (requires some help but able to walk unassisted), 4=moderately severe disability (unable to handle bodily needs without assistance and unable to walk unassisted), 5=severe disability (requires constant nursing care and attention) and 6=death. There were significant differences in the overall distribution of the scores between the IAT and IVT groups at 7 days ( $\chi^2$  test,  $p<0.001$ ), 90 days ( $\chi^2$  test,  $p<0.001$ ) and 180 days after onset ( $\chi^2$  test,  $p<0.001$ ). In the IVT group, there were no patients with the score of 0–2 at 7 days, of 0–1 at 90 days and of 0 at 180 days.

## Study outcomes

Primary outcomes included the rate of recanalization on CTA or MRA at 24 hours after procedure and survival at 7 days after symptom onset. Other outcomes included survival at 90 and 180 days after onset and mRS and NIHSS scores 7, 90, and 180 days post-ACI, with mRS score  $\leq 2$  indicating functional independence.<sup>23</sup> The safety outcome of interest was symptomatic and asymptomatic hemorrhagic transformation within 7 days of ACI.

## Follow-up

All patients received clinical evaluation (including assessment of NIHSS and mRS scores) at baseline, 24 hours, and 7 days or at discharge, if earlier. A stroke neurologist, who was blinded to the treatment groups, conducted the follow-up interviews from April 21, 2008 to December 31, 2014 at 3-month intervals by telephone with the patient, proxy, or healthcare provider, followed by assessment of the mRS and NIHSS scores in clinic or at a medical center (if hospitalized) by clinicians who were unaware of the treatment group.

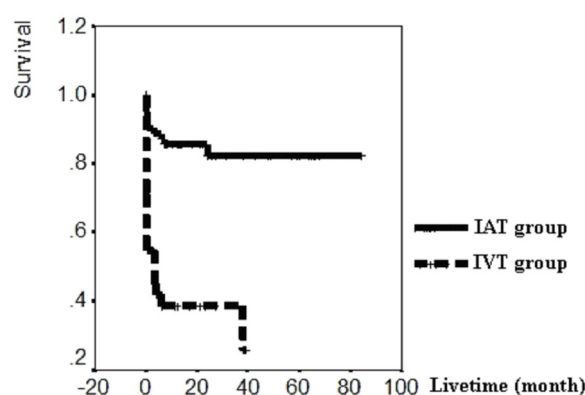
## Statistical analysis

Continuous data were summarized as mean $\pm$ SD or median (IQR) if the data were not normally distributed. Categorical data were summarized using numbers and percentages. Student's independent sample t-test, Mann-Whitney U test, and Pearson's  $\chi^2$  test were used as appropriate to assess the differences between the IVT and IAT groups. Logistic regression was used to analyze the survival with treatment group and mRS score (which was converted into a dichotomous variable to separate patients' scores of 0–2 from those with mRS scores  $\geq 3$ ). The changes in survival rate and NIHSS score over time (7, 90, and 180 days) were analyzed using generalized estimating equations (GEE). Kaplan-Meier and Cox regression models were used to analyze survival and prognostic factors, respectively. The statistical significance level for all the tests was set at a  $p<0.05$ . All

**Table 4** Generalized estimating equation (GEE) results of NIHSS and survival rate

	NIHSS				Survival rate			
	Estimated mean (SE)	GEE coefficient (SE)*	Wald $\chi^2$	p Value	Estimated mean (SE)	GEE coefficient (SE)*	Wald $\chi^2$	p Value
Group			7.4	0.007			17.6	<0.001
IVT	14.5 (1.5)	Ref.	-	-	47.3 (8.4)	Ref.	-	-
IAT	9.8 (0.9)	-3.1 (1.6)	4.0	0.047	88.3 (3.9)	2.0 (0.6)	13.2	<0.001
Time			40.8	<0.001			8.7	0.013
7 days	15.3 (0.8)	Ref.	-	-	77.1 (5.0)	Ref.	-	-
90 days	11.0 (1.1)	-3.1 (1.8)	3.0	0.082	73.1 (5.3)	-0.3 (0.2)	2.1	0.145
180 days	10.1 (1.1)	-3.9 (1.9)	4.3	0.038	65.9 (5.8)	-0.7 (0.3)	5.8	0.016
Group*time			2.0	0.362			0.3	0.877
IVT-7 days	16.8 (1.3)	Ref.	-	-	54.8 (8.9)	Ref.	-	-
IVT-90 days	13.7 (1.9)	Ref.	-	-	48.4 (9.0)	Ref.	-	-
IVT-180 days	13.0 (1.9)	Ref.	-	-	38.7 (8.7)	Ref.	-	-
IAT-7 days	13.8 (0.9)	Ref.	-	-	90.3 (3.8)	Ref.	-	-
IAT-90 days	8.3 (0.9)	-2.4 (1.9)	1.6	0.208	88.7 (4.0)	0.1 (0.2)	0.1	0.725
IAT-180 days	7.2 (1.0)	-2.7 (2.0)	1.8	0.175	85.5 (4.5)	0.2 (0.4)	0.3	0.609

\*The link functions used in GEE model of NIHSS and survival rate are linear and binary logistic, respectively. IAT, intra-arterial treatment; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.



**Figure 2** Survival analysis of Kaplan-Meier between intra-arterial treatment (IAT) and intravenous thrombolysis (IVT) groups. Patients in the IAT group had a longer survival time than those in the IVT group (log-rank test,  $\chi^2=26.9$ ,  $p<0.001$ ).

analyses were performed using IBM SPSS V.20 (SPSS Statistics, IBM, Somers, New York, USA).

## RESULTS

Of the 1395 inpatients with hypertension and ACI in the medical records, 658 patients with occlusions of the anterior circulation were omitted from the study for not registering within 6 hours, and 458 patients with occlusions of the posterior circulation were omitted from the study for not registering within 12 hours due to not arriving at the hospital in time. Thus, 279 patients met the inclusion criteria of having received intravenous thrombolysis with intravenous alteplase or endovascular treatment. Of these, 181 patients with mild-to-moderate ACI were omitted from the study for having either an mRS score  $<5$  or an NIHSS score  $<17$  (ie, they failed to meet the first study entry criterion of having both a baseline mRS score  $\geq 5$  and an NIHSS score  $\geq 17$ ), and five patients were omitted from the study for undergoing intravenous alteplase plus intra-arterial mechanical thrombectomy. Finally, a total of 93 patients (62 in the IAT group and 31 in the IVT group) were eligible for this study (see online supplementary figure 2, flow chart of the recruitment of patients). Baseline characteristics are presented in table 1. The only difference in characteristics between the IAT and IVT groups was that the patients in the IAT group started treatment significantly later than those in the IVT group: other baseline characteristics were similar between the two treatment groups. Additionally, online supplementary table 1 compares the baseline characteristics of patients enrolled at the two participating

hospitals. There were significant between-group differences in the baseline DBP, HDL, history of diabetes, and the site of occlusion.

Of the 1395 inpatients with hypertension and ACI in the medical records, a total of 93 patients were eligible for this study (62 in the IAT group and 31 in the IVT group). Eleven patients (11.8%) underwent CTA examination before and after the procedure (seven in the IAT group vs four in the IVT group), and other patients received a head MRA assessment before and after treatment (55 in the IAT group vs 27 in the IVT group). The surviving patients were followed up for 6–84 months.

## Intervention

In the intervention group (IAT group), the time from symptom onset to groin puncture was a median of 5 hours (IQR 4.0–6.3). Intra-arterial thrombolysis alone was deployed in 11 patients (17.7%), the stent retriever alone in 23 patients (37.1%), stent retriever plus balloon expansion in 18 patients (29.0%), and stent retriever and intra-arterial thrombolysis plus balloon/stenting in 10 patients (16.1%). A total of 10 patients with ACI (16.1% patients) with intracranial and/or extracranial arterial stenoses received a total of 16 stents. Among the 62 patients with IAT, 48 patients (77.4%) achieved revascularization, including 36 patients (58.1%) with TICI grade 3 and 12 patients (19.4%) with TICI 2b. Online supplementary table 2 shows the TICI scores and stenting data for the IAT group and online supplementary figures 1 and 2 show imaging data of typical IAT and IVT cases, respectively. Regarding the solitaire retriever, balloon angioplasty, and stent angioplasty subgroups, the solitaire retriever treatment increased the frequency of functional independence (mRS  $\leq 2$ ) at 90 days after onset compared with balloon and stent treatment ( $p=0.035$ ); however, since more patients recovered in the other two subgroups, no significant difference of functional independence was found between the three subgroups at 180 days after operation. Additionally, since more patients died in the other two subgroups, the solitaire retriever treatment exhibited a higher frequency of survival than the other two subgroups at 180 days after the procedure. All other parameters were similar between the three subgroups at each time point (table 2).

## Primary outcomes

Of the 93 patients in the study, 82 (88.2%) underwent repeated head MRA, and 11 patients (11.8%) underwent repeated head CTA examinations beginning 24 hours after procedures. Successful reperfusion, defined as grade 3, was significantly more likely in IAT than in patients with IVT ( $p<0.001$ ). The survival rate was also significantly higher in the IAT group ( $p<0.001$ ) (table 3).

## Other outcomes

Multimodal IAT significantly increased the frequency of survival at both 3 and 6 months after ACI (see table 3). The NIHSS scores for surviving patients did not show a significant difference between the IAT and IVT groups at 7 days, but showed a significant difference at 90 and 180 days ( $p=0.022$  and  $p=0.016$ , respectively). Significant differences in the mRS score were also noted (table 3,

**Table 5** Cox regression for the survival of patients with ACI after IAT and IVT treatment

Variables	Coefficient	p Value	HR	95% CI for OR
Duration	0.4	$<0.001$	1.4	(1.2 to 1.8)
IAT	−2.3	$<0.001$	0.1	(0.0 to 0.4)
Recanalization	−2.1	$<0.001$	0.1	(0.0 to 0.4)

ACI, acute cerebral infarction; IAT, intra-arterial treatment; IVT, intravenous thrombolysis.

figure 1). GEE modeling showed that both the NIHSS score and survival rate gradually declined with time. In general, patients with IVT had higher NIHSS scores, while patients with IAT had higher survival rates (all  $p < 0.05$ ) (table 4).

Kaplan-Meier analysis showed that overall survival was significantly longer for patients in the IAT group compared with those in the IVT group (figure 2). Multivariate Cox regression revealed that multimodal IAT and revascularization were independent predictors of longer survival (HR=0.1,  $p < 0.001$  and HR=0.1,  $p < 0.001$ , respectively) and that longer duration from symptom onset to the beginning of treatment was associated with shorter survival (HR=1.4,  $p < 0.001$ ) (table 5); other covariates, including age, gender, diabetes, smoking, drinking, occluded artery (MCA, ICA, or BA), SBP, DBP, TC, TG, HDL, LDL, and hemorrhage transformation, did not show significant differences with any outcome variables.

### Safety

The rates of both symptomatic and asymptomatic hemorrhagic transformation did not differ significantly between the IAT and IVT groups (table 3).

### DISCUSSION

Our results show that we can achieve favorable results with regard to revascularization rates, survival, and functional recovery using multimodal IAT compared with IVT in hypertensive patients with severe ACI caused by blockage of large cerebral vessels. The results also confirm the benefits of endovascular treatment reported in recent trials.<sup>9 12–16</sup> The association between longer survival and the revascularization obtained using multimodal IAT was consistent with the results of the Solitaire with the Intention for Thrombectomy Primary Endovascular Treatment (SWIFT PRIME) trial and the Japan RESCUE registry study. The increase in early reperfusion led to a reduction in cerebral infarction growth and substantial clinical benefit in more patients surviving with functional independence at 6 months. This reduction in cerebral infarction growth is likely due to the salvage of the ischemic penumbra.<sup>15</sup> The results were obtained despite the longer time to treatment in the IAT group.

The major strength of our study is that we focus on a particularly high-risk group of patients with severe ACI (who usually suffer high morbidity and mortality) and show that we achieve better results in this patient population using multimodal IAT, although regarding the patients with mild-to-moderate ACI, some published studies did not support the use of IAT over IVT.<sup>10 11</sup> The eligible patients were all patients with hypertension and severe ACI caused by large vessel occlusion. The baseline median NIHSS score was 22.6, which was higher than in recent randomized controlled trials,<sup>12–16</sup> and also allowed us to focus on a particularly high-risk group of patients. Such patients usually have a low probability of a good clinical outcome and have a higher risk of symptomatic hemorrhage transformation and malignant edema and are more likely to have multiple vessels with arteriosclerosis and proliferative plaque formation that are impossible to dissolve with thrombolitics alone.<sup>24 25</sup> Therefore, in these cases, IVT is often associated with poor recanalization and clinical outcomes.

The high percentage of patients in our study who underwent multiple intra-arterial treatment modalities was associated with a frequency of revascularization, survival, and functional recovery that was higher than that seen in other studies.<sup>9 16</sup> Moreover, through subgroup analysis of the IAT group in the current study, the solitaire retriever treatment showed slightly better clinical outcomes compared with balloon and stent angioplasty. These results indicate that multimodal IAT was favorable for patient with severe ACI with hypertension.

There are several limitations in our study; first, our study is a retrospective chart review with a small number of patients, not a multicenter randomized controlled trial with a protocol in place. One consequence is that we included patients with a diagnosis of hypertension based on either three consecutive elevated morning blood pressure measurements after admission or a history of hypertension; thus, we defined hypertensive acute stroke based on chronic hypertension as well as hypertension in response to the stroke. Second, our study compared IVT with multimodal IAT alone, not with the intravenous alteplase plus intra-arterial treatment. Third, selection bias was present: the IVT group was treated for up to 4.5 hours, and the IAT group was treated for up to 6 hours in the anterior circulation and up to 12 hours in the posterior circulation. However, IAT did better even when the intervention occurred later, which indicated a favorable outcome for IAT. Fourth, there is also a bias in medical treatment postprocedure: the stented group had aspirin plus clopidogrel, and others had either aspirin or clopidogrel, which may influence the hemorrhage rates after the procedure. Fifth, the patients from the two centers in this study had significant differences in baseline DBP, baseline HDL, history of diabetes, and the sites of occlusion; however, these differences in the two patient groups highlight the fact that in the community, even with different operators/hospitals, IAT remains superior.

Among the hypertensive patients with severe acute ischemic stroke caused by large-vessel occlusion, multimodal IAT was safe and effective in increasing the frequency of revascularization and survival, as well as the proportion of patients with a functional outcome 6 months after stroke. Future studies should be undertaken to prove our results in a randomized controlled trial and to analyze results in other subgroups of patients with stroke, including those with cardioembolic stroke.

**Contributors** We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. ZT designed the study and wrote the protocol. GL, ZT, LL and CC performed research/study. ZT, SL and GL contributed important cases (reagents). ZT, GL, SL and YL managed the literature searches and analyses. ZT and SL undertook the statistical analysis. ZT and YS wrote the first draft of the manuscript. ZT, GL, YL and CC collected data. ZT and YS obtained funding. ZT, GL and SL took overall responsibility. ZT and YS contributed the funding of the manuscript.

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