Intravenous Thrombolysis for Acute Mild Ischemic Stroke Patients: Higher ABCD2 Score Associated with Better Outcome

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Abstract

Background: Up to 30% of patients with mild ischemic stroke suffer neurologic deterioration. However, optimal medical approaches of such patients remain controversial given the efficacy and safety of intravenous thrombolysis (IVT). The purpose of this study was to evaluate whether patients with acute mild stroke stratified with ABCD2 score (the risk of stroke on basis of age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus) could benefit from IVT. **Methods:** Among 3321 patients with a final diagnosis of acute ischemic stroke, we retrospectively included 224 patients identified with acute mild neurologic deficits (National Institution of Health Stroke Scale, NIHSS ≤ 5) treated with or without IVT. Odds ratios (OR) with their confidence intervals (CI) for outcomes between groups were assessed by using multivariable binary logistic regression analyses. And the heterogeneity of treatment effect magnitude for excellent outcome at 90d (modified Rankin Scale [mRS] 0-1) was estimated in different subgroups. **Results:** A total of 224 cases were enrolled, 106 receiving IVT and 118 treated with secondary stroke prevention strategies alone. At 7d, 30 (28.3%) patients with IVT treatment versus 16 (13.6%) patients not receiving IVT achieved significant improvement (≥ 4 -point NIHSS score decrease or complete resolution; OR, 2.448; 95%CI, 1.204-4.977; $P=0.013$). At 90d, excellent outcome was achieved in 83 (78.3%) patients treated with IVT versus 77 (65.35%) patients without IVT treatment (OR, 3.156; 95%CI, 1.526-6.528; $P=0.002$), especially in those with ABCD2 score ≥ 5 (OR, 2.768; 95%CI, 1.196-6.406; $P=0.017$) and with stroke subtype of large artery atherosclerosis (OR, 5.616; 95%CI, 1.080-29.210; $P=0.040$). Besides, 7(6.6%) IVT-treated patients versus 2 (1.7%) non-IVT-treated patients developed intracranial hemorrhage (ICH; $P=0.359$), among these only 1 (0.9%) was symptomatic ICH in IVT group. **Conclusions:** For acute mild ischemic stroke patients, we reassured the safety and especially the efficacy of IVT at 7- and 90-days. Patients with 5 or more of ABCD2 score and stroke subtype of large artery atherosclerosis might benefit more from IVT.

Background

Mild stroke accounts for approximately two thirds of acute ischemic stroke patients in population-based studies[1, 2]. Nevertheless, minor neurological deficiency or rapidly improving symptoms are the most common reasons for withdraw from IVT in otherwise guideline-based eligible patients[3]. In addition, mild stroke is considered to be the beginning of a potential dynamic process. Previous data indicated that 30% of such patients had persistent disability at 90d[4], and the risk of recurrent stroke at 90d, 1 year and 5 years were 3.7%, 5.1% and 9.5%, respectively[5, 6].

Although the proportion of thrombolytic therapy for mild stroke patients has increased over the past decade, the efficacy and safety of recombinant tissue plasminogen activator (rt-PA) remains controversial. A series of studies suggested patients with mild deficiency could benefit from IVT[7-11]. Currently, the American Stroke Association gives a level I (strong) and IIb (weak) evidence-based score respectively for IVT in patients with mild disabling and nondisabling ischemic stroke symptoms within 3h[12]. But there were also studies indicating no significance in the efficacy between IVT and antiplatelet therapy in patients with mild stroke[13, 14], especially in those with non-disabling deficiency[14]. And

the patient treated with IVT was not recommended given antithrombotic therapy within 24 hours, even though an aggravation of the condition. In consideration of the controversial therapeutic decision-making, it is necessary to screen high-risk mild stroke patients for IVT.

It is well known that the ABCD scoring system is designed for evaluating the likelihood of recurrent stroke in transient ischemic attack and minor stroke patients[6, 15, 16]. However, it is not clear the effectiveness of ABCD₂ score to evaluate the prognosis in patients with mild stroke.

The purpose of this observational study was to investigate whether patients with acute mild stroke symptoms (NIHSS score $\leq$ 5) could achieve 7- and 90-day favorable outcome from intravenous rt-PA therapy by comparing with patients treated with timely secondary stroke prevention strategies not receiving rt-PA. We also hypothesized that ABCD₂ score might be related to the prognosis of mild stroke patients.

Methods

Study Design

This study was designed as a retrospective study evaluating the efficacy and safety of IVT administered within 4.5 hours of symptom onset. Consecutive acute ischemic stroke (AIS) patients with minor-to-mild stroke symptoms (NIHSS score $\leq$ 5) were enrolled from our hospital between August 2016 and May 2018. Ethical approval for this study was obtained from the First Affiliated Hospital of Soochow University Institutional Review Board (No. 2019021). And all data were analyzed anonymously.

Patients Selection

Eligible cases were collected using the following inclusion criteria: (1) Clinical final diagnosis of AIS with baseline NIHSS score 0 to 5; (2) Age 18 years or older; (3) Time from symptom onset within 4.5h for rt-PA group, however, it could be extended up to 24 hours after symptom onset in non-rt-PA group; (4) Available for a telephone interview at 90d. The exclusion criteria were as follows: (1) Clinical final diagnosis of transient ischemic stroke (TIA); (2) Pre-stroke mRS score of $\geq$ 2; (3) ICH on baseline computed tomography, and other contraindications to IVT and antithrombotic therapy.

Patient Management

All patients were given appropriate standardized treatment in accordance with the guidelines[12]. Participants were divided into two groups according to different approaches about the management of mild stroke patients: (1) rt-PA group: Intravenous rt-PA within 4.5 hours of AIS onset or last known well time (0.9 mg/kg, maximum dose 90 mg with initial 10% of total dose given as bolus during 1 minute), followed by appropriate secondary stroke prevention strategies; (2) Non-rt-PA group: Optimal secondary

stroke prevention strategies within 24h from AIS onset: including initiation of dual antiplatelets among patients with NIHSS $\leq$ 3 (clopidogrel 75 mg per day for 90d + aspirin 100 mg per day for the first 3 weeks); clopidogrel 75mg/ aspirin 100mg per day; or anticoagulation agents in the event of cardioembolism, and other measures such as statins and antihypertensive medication, etc.

Patient Data Collection

Baseline demographic and clinical information were collected by experienced stroke neurologists: including age, gender, previous history (hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary heart disease, previous stroke or TIA and current smoking), medication history, blood pressure at baseline, laboratory data, time from symptom onset, stroke severity (assessed by NIHSS score at admission and 7d), ABCD₂ score (chosen due to easiest-to-manipulate in emergency room), disabled stroke[14], and stroke subtype (assessed using TOAST classification [Trial of Org 10172 in Acute Stroke Treatment])[17]. Neurological imaging information was collected at baseline, 24-36h, 7d or discharge if sooner in stroke unit, including infarct location, severity of responsible artery stenosis, and intracranial hemorrhage transformation.

Clinical Assessment and Definition of Functional Outcomes

The follow-up was conducted by two trained neurological doctors who were blinded to the baseline information via telephone or face-to-face interviews. (1) Efficacy outcomes: The achievement of an mRS of 0 to 1 at 90d was primary outcome defined as excellent outcome, and an mRS of 0 as perfect outcome. Significant improvement was referred as complete resolution of the neurologic deficit or an improvement of at least 4 points over baseline NIHSS score[18]. (2) Adverse outcomes: Early neurological deterioration (END) was defined as a NIHSS score increase of 2 or more within 7d after symptom onset excluding any CT- or MRI-documented ICH[19]. sICH was defined as CT-based ICH within 7d with a NIHSS score increase of at least 4 or death[20]. The recurrent ischemic stroke within 3 months was assessed by stroke specialists.

Statistical Analysis

Categorical variables are expressed as numbers (%). Continuous variables are expressed as mean (standard deviation [SD]) in the case of normal distribution, otherwise as median (interquartile range [IQR]), and the normality of distributions was evaluated by histograms and the Shapiro–Wilk test. The between-group differences in baseline characteristics were assessed by univariate analysis as follows: continuous variables were compared with the Student *t* test or Mann-Whitney *U* test as appropriate, while categorical variables were compared with Fisher's exact test or chi-square test. Adjusted for intravenous

rt-PA treatment and variables with P value < 0.1 in univariate analysis for different functional outcomes, multivariate logistic regression analysis was used to determine the independent predictors for all prognosis, especially the relationship between intravenous rt-PA treatment and clinical outcomes. Moreover, receiver operator characteristic curves (ROCs) were performed to estimate the best cut-off values, sensitivity and specificity of baseline NIHSS score and ABCD₂ score for predicting adverse outcomes. According to the best cut-off values, we intended to estimate the heterogeneity of therapeutic effect magnitude for excellent outcome stratified by baseline NIHSS score (≤ 3 versus > 3), stroke subtype assessed by TOAST classification, disabling neurologic deficits (yes versus no), and baseline ABCD₂ score (≤ 5 versus ≥ 5).

The α -level of significance was $P < 0.05$ (bilateral). All analyses were performed using the SPSS software version 25.0.

Results

Population and Baseline Characteristics

In the First Affiliated Hospital of Soochow University, a total of 3321 patients with a final diagnosis of AIS were derived from the Electronic Patient Record system between August 2016 and May 2018. And 808 patients with NIHSS score ≤ 5 were extracted from the cohort. Among them, 584 were excluded on the basis of inclusion and exclusion criteria, resulting in 224 participants enrolled in the study. According to different therapeutic approaches, 106 patients were included in the rt-PA group and 118 patients in the non-rt-PA group.

The median age of enrolled patients was 66.00 (*IQR*, 59.00-74.00) and 73 (32.6%) were women, with the most common medical risk factors being hypertension (71.4%) and hyperlipoidemia (45.5%). The median baseline NIHSS score and ABCD₂ score were 3.00 (*IQR*, 2.00-4.00) and 5.00 (*IQR*, 5.00-6.00), respectively. Among the studied patients with mild stroke, the most common stroke subtype was small vessel occlusion (37.5%) followed by large artery atherosclerosis (33.0%), with other/undetermined etiology (15.2%) and cardioembolism (14.3%) less frequent.

In the rt-PA group, patients had a significantly higher proportion of atrial fibrillation (18.9% vs 7.6%, $P = 0.012$), while the proportion of hyperlipidemia was significantly lower than that in patients not receiving rt-PA treatment (35.8% vs 54.2%, $P = 0.006$). In addition, there was no significant difference in other aspects summarized in Table 1 ($P > 0.05$), indicating that the two groups were generally balanced and comparable.

Univariate Analysis of Functional Outcomes at 90 Days

Among the enrolled 224 patients with acute mild stroke, excellent outcome at 90d was obtained in 160 (71.4%) patients and poor outcome in 64 (28.6%) patients. In univariate analysis, patients with excellent outcome at 90d had a significantly higher percentage of receiving rt-PA treatment than those with poor outcome (51.9% vs 35.9%, $P=0.031$). Also, female, higher baseline NIHSS score and ABCD₂ score, history of diabetes mellitus and antidiabetic agents, higher level of FPG and TC, stroke subtype, and severity of responsible artery stenosis were associated with poor outcome (Table 2).

Multivariate Analysis Between Covariates and Different Clinical Outcomes

After adjusting for confounders in multivariable logistic regression analysis, intravenous rt-PA treatment was independently correlated with both excellent and perfect outcome at 90d, also with significant improvement at 7d. But we didn't detect any independent association between intravenous rt-PA treatment and adverse outcomes showed in Figure 1. Table 3 illustrated the independent predictors for different clinical outcomes. Excellent outcome at 90d was achieved in 83 (78.3%) patients treated with rt-PA compared with 77 (65.3%) patients without rt-PA treatment, with an adjusted OR of 3.156 (95%CI, 1.526-6.528; $P=0.002$) after controlling for the effects of male (OR, 3.151; 95%CI, 1.577-6.293; $P=0.001$), worse initial NIHSS score (OR, 0.551; 95%CI, 0.413-0.735; $P<0.001$), more serious of responsible artery stenosis, and higher level of FPG. Meanwhile, in rt-PA group, the proportion of excellent outcome was 89.9% within 3h after symptom onset, and 73.1% within 3-4.5h. While the difference was not statistically significant ($P=0.17$) (data not shown). Besides, worse stroke severity (OR, 0.652; 95%CI, 0.512-0.831; $P=0.001$), history of diabetes mellitus and higher level of high-density lipoprotein cholesterol (HDL-C) were negatively associated with perfect outcome. We detected significant improvement at 7d in 30 (28.3%) patients with rt-PA treatment versus 16 (13.6%) patients without rt-PA treatment, which was independently related with male and worse stroke severity (OR, 0.740; 95%CI, 0.558-0.983; $P=0.038$). The rate of END within 7d was 10.2% in patients untreated with rt-PA, whereas 13.2% in patients treated with rt-PA, with no statistically significant difference between two groups ($P=0.472$). It is worthy noting that higher ABCD₂ score was independently associated with END at 7d (OR, 2.293; 95%CI, 1.396-3.766; $P=0.001$). Any ICH within 7d, occurred in 7 (6.6%) patients treated with rt-PA compared with 2 (1.7%) patients without rt-PA treatment, with no significant association with intravenous thrombolysis ($P=0.359$). Among them, only 1 (0.9%) was sICH in rt-PA group. Older age, high level of systolic blood pressure at admission and worse stroke severity were independently correlated with ICH. While the recurrent ischemic stroke in 90d was less frequent in patients treated with rt-PA (2.8%) than the other group (5.9%). Only male and both circulation infarction were strongly related with incidence of recurrent ischemic stroke.

ROC Analysis for Predictive Efficacy of Adverse Outcomes

In ROC curve analysis, the best cut-off value of the baseline NIHSS score was 3.5 to differentiate between excellent and poor outcome (AUC, 0.675; 95%CI, 0.594-0.756; $P<0.001$), presenting 57.8% sensitivity and 75.0% specificity. While, the baseline ABCD₂ score best cut-off value of 4.5 was used for evaluating END (AUC, 0.707; 95%CI, 0.606-0.809; $P=0.001$), with 69.2% sensitivity and 64.1% specificity.

Association Between Subgroups and Excellent Outcome

According to the best cut-off values of independent predictors, we carried out multivariate analysis of excellent outcome in subgroups. It was showed that patients treated with rt-PA could still obtain a higher 90-day excellent outcome rate than that without rt-PA, even if NIHSS score ≤ 3 (OR, 3.603; 95%CI, 1.249-10.392; $P=0.018$). In patients of ABCD₂ ≥ 5 , intravenous rt-PA treatment was independently associated with higher proportion of excellent outcome at 90d, with 57 (72.2%) patients receiving rt-PA versus 58 (62.4%) not receiving rt-PA (OR, 2.768; 95%CI, 1.196-6.406; $P=0.017$). For patients with ABCD₂ score ≤ 5 , significance of treatment effect was not observed between two groups. Among patients with stroke subtype of large artery atherosclerosis, the excellent outcome rate at 90d in rt-PA group (63.9%) was significantly higher than that in the other group (52.6%) with an adjusted OR of 5.616 (95%CI, 1.080-29.210; $P=0.040$). Besides, in patients with disabling stroke, we didn't detect independent association between rt-PA treatment and excellent outcome at 90d. (Figure 2).

Discussion

Our study implied a high proportion of 78.3% acute mild ischemic stroke (NIHSS score ≤ 5) patients receiving intravenous rt-PA within 4.5 hours achieved excellent outcome (mRS 0-1) at 90d, and 28.3% of such patients had significant improvement at 7d. The 90d excellent outcome rate reached 90.3% even if in patients with NIHSS score ≤ 3 . And the encouraging results were both detected in the 0-3h (83.9%) and 3-4.5h (73.1%) time windows. The above proportion was significantly higher than that of the patients without IVT, among them only 1 case developed sICH in patients with intravenous rt-PA treatment, indicating IVT being relatively effective and safe for patients with mild neurological deficits. Notably, we found that patients with mild stroke whose ABCD₂ score ≥ 5 and stroke subtype of large artery atherosclerosis could benefit more from IVT.

A series of randomized studies[7, 14], systematic review[8-10] and observational cohorts[11, 13] indicated controversial results regarding the efficacy of IVT among patients with acute mild ischemic stroke. The post hoc analysis in a rigorously selected sample (restricted to 106 participants with a baseline NIHSS score ≤ 5 within 3 hours from symptom onset) of the third International Stroke Trial (IST-3) suggested encouraging results of intravenous rt-PA efficacy in mild ischemic stroke (84% rt-PA versus 65% control; adjusted odds ratio, 3.31; 95% CI, 1.24–8.79; $P=0.03$)[7], which is consistent with our study and most post previous data[8-11]. Nevertheless, a large observational cohort from China suggested that

intravenous rt-PA might potentially benefit patients with NIHSS score ≤ 5 within 4.5 hours from symptom onset, with no statistical significance (76% rt-PA versus 69.5% control; odds ratio, 1.48; 95% CI, 0.91–2.43; $P=0.12$) [13]. The difference in efficacy of IVT might be associated with the different time window selection, various definition of mild stroke and better secondary stroke prevention measurements.

As for the safety of intravenous rt-PA in mild stroke, we detected 7 (6.6%) receiving intravenous rt-PA patients occurred ICH within 7d compared with the lower rate of 1.7% in non-rt-PA group, yet among these only 1 (0.9%) developed sICH from rt-PA group, lower than the proportion of 1.8%-4.1% previous studies had reported [14, 21, 22]. The significant association between post-IVT ICH with older age, worse stroke severity and higher admission glucose level was reported in a systematic review from 55 studies [23], similar with our study data. The incidence of sICH in a large single-center cohort [24] stratified by baseline NIHSS score (≤ 6 versus ≥ 6) was 2.0% and 8.1% ($P=0.001$), respectively, while the difference was not detected with increasing NIHSS score within the range of 0 to 5 ($P=0.51$) [21], indicating that intravenous rt-PA is relatively safe but not risk-free in mild stroke patients.

Previous studies suggested that TOAST classification [13], disability [14], abnormal ischemic perfusion [25] and penumbra [26] can be used to screen high-risk patients with mild stroke. Currently, the preliminary results of Potential of rt-PA for Ischemic Strokes with Mild Symptoms (PRISMS) [14], a double-blind, multicenter, randomized controlled trial, revealed that likelihood of excellent outcome at 90d didn't increase among mild nondisabling AIS patients receiving IVT treatment, yet a higher risk of sICH. However, the early termination with only 313 participants enrolled might preclude the definitive conclusions. While our study detected significant difference for excellent outcome in patients with nondisabling deficits. The disabling deficit is commonly defined as follows: complete hemianopia (NIHSS-3 ≥ 2), severe aphasia (NIHSS-9 ≥ 2), neglect NIHSS-11 ≥ 1), limb weakness that cannot resist gravity (NIHSS-5/6 ≥ 2), functional impairment with NIHSS > 5 , or any potential disabling deficit judged by experienced physician [14]. Nevertheless, the NIHSS scale may not be adequate to evaluate severity of mild stroke, especially in posterior circulation AIS patients [27], hence considerable patients are regarded as nondisabling deficiency, resulting in unfavorable outcome. So accurate description of disabling neurological deficits is warranted urgently to screen high-risk mild AIS patients.

Our study demonstrated that acute mild stroke with ABCD₂ score ≥ 5 , a fresh perspective to screen appropriate patients, might potentially benefit more from intravenous rt-PA treatment. ABCD₂ score was intended to aid clinical management and estimate the risk of stroke recurrence in patients with TIA and minor stroke [15]. In addition, ABCD₃-I score (range 0-13, addition of dual TIA within 7d, ipsilateral carotid artery stenosis $\geq 50\%$ and positive brain imaging) showed better validation for prediction of early and 90-day stroke recurrent risk, with clinical presentation (C), symptom duration (D) and cerebral/carotid imaging (I) being the most essential components [16, 28, 29]. Recent trial revealed the ABCD₂ score of 4 and more in TIA or minor stroke was significantly associated with longer-term risk of another stroke [6]. Also, these scores were used to select patients for intensive therapy [30, 31]. However, it remains unclear regarding the validation of the risk scores to screen high-risk candidates for intravenous rt-PA among mild stroke patients, so that further investigation in randomized trials or larger observational studies is needed.

Besides, in clinical practice, physicians can as well refer to the stroke etiology of large artery atherosclerosis[13] and presentation of disability[12] to assist thrombolytic decision-making.

Thus, further investigations are warranted. Mild and Rapidly Improving Stroke Study (MaRISS; observational trial; NCT02072681) and Antiplatelet vs Rt-PA for Acute Mild Ischemic Stroke (ARAMIS; randomized, placebo-controlled trial; NCT03661411) are two ongoing trials investigating the safety and particularly the efficacy of intravenous rt-PA in patients with acute mild stroke.

The non-randomized design due to retrospective study is the most notable limitation of our research. Although, the baseline characteristics between two groups were matched generally, with significant difference only in history of atrial fibrillation and hyperlipemia, the well-known limitations of observational study still not be avoided. And the small sample size of 224 enrolled subjects in this single-center study limited the power to assess the efficacy and safety of IVT among mild stroke patients, resulting in the inadequacy to generalize the results of our research to nation-wide population with mild stroke. So, well-designed multicenter randomized clinical trials are needed urgently.

Conclusions

A substantial proportion of patients deemed mild stroke ($\text{NIHSS} \leq 5$) with intravenous rt-PA therapy has excellent outcome both at 7- and 90-days, especially among patients with 5 or more of baseline ABCD_2 score and stroke subtype of large artery atherosclerosis. While, accurate identification of high-risk stroke is so essential to screen patients with mild deficiency for IVT, that further researches are warranted. In conclusion, given the significant percentage of excellent outcome and low risk of sICH, our results reassure the efficacy and safety of IVT therapy for acute mild ischemic stroke patients.

Abbreviations

ABCD_2 score: The risk of stroke on basis of age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; $\text{ABCD}_3\text{-I}$ score: Addition of dual symptom onsets within 7d, ipsilateral carotid artery stenosis $\geq 50\%$ and positive brain imaging on the basis of ABCD_2 score; AIS: Acute ischemic stroke; ARAMIS: Antiplatelet vs rt-PA for acute mild ischemic stroke; CI: Confidence interval; END: Early neurological deterioration; FPG, fasting plasma glucose; HDL-C high-density lipoprotein cholesterol; ICH: Intracranial hemorrhage; IQR: Interquartile range; IVT: Intravenous thrombolysis; LDL-C, low-density lipoprotein cholesterol; MaRISS: Mild and rapidly improving stroke study; mRS: Modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; PRISMS: Potential of rtPA for ischemic strokes with mild symptoms; rt-PA: Recombinant tissue plasminogen activator; SD: Standard deviation; sICH: Symptomatic intracranial hemorrhage; TC, total cholesterol; TG, total glyceride; TIA: Transient ischemic stroke; TOAST: Trial of org 10172 in acute stroke treatment.

Declarations

Ethics approval and consent to participate

The use of data analysis was legally approved by the First Affiliated Hospital of Soochow University Institutional Review Board (No. 2019021). This research was performed in accordance with the tenets of the Declaration of Helsinki as amended in 2008.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QF, XC and YK designed this study. RL and CH collected and analyzed the patient data, and were the major contributor in writing the manuscript. JZ, LZ, RL, CH, ZL and XL conducted the clinical assessments and follow-up of participants. All authors contributed to creating this manuscript and improved the final version.

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Tables

Table 1 Baseline Characteristics of Patients with Mild Stroke According to therapeutic approach.

Characteristics*	rt-PA (n= 106)	Non-rt-PA (n= 118)	P value§
Age, y, median (<i>IQR</i>)	66.00(59.00-74.00)	66.00(59.00-74.00)	0.850
Female	28(26.4)	45(38.1)	0.062
Medical history			
Hypertension	76(71.7)	84(71.2)	0.933
Diabetes mellitus	30(28.3)	27(22.9)	0.352
Hyperlipoidemia	38(35.8)	64(54.2)	0.006
Atrial Fibrillation	20(18.9)	9(7.6)	0.012
Coronary heart disease	8(7.5)	10(8.5)	0.799
Previous stroke/TIA	15(14.2)	17(14.4)	0.956
Current smoking	42(39.6)	36(30.5)	0.153
Medications prior to onset			
Antihypertension agents	61(57.5)	68(57.6)	0.990
Antidiabetic agents	23(21.7)	20(16.9)	0.368
Antiplatelet agents	13(12.3)	12(10.2)	0.619
Anticoagulant agents	3(2.8)	2(1.7)	0.903
Laboratory data, mmol/L			
FPG, median (<i>IQR</i>)	5.32(4.76-6.28)	4.99(4.58-5.99)	0.100
TC	4.33±0.95	4.35±0.88	0.898
LDL-C	2.56±0.80	2.52±0.72	0.695
HDL-C, median (<i>IQR</i>)	1.17(1.01-1.27)	1.20(1.06-1.36)	0.065
TG, median (<i>IQR</i>)	1.29(0.93-1.77)	1.23(0.94-1.73)	0.731
Admission blood pressure, mmHg			
Systolic blood pressure	153.57±21.26	149.31±18.95	0.115
Diastolic blood pressure	85.54±13.39	83.87±12.16	0.331
Baseline clinical profiles			
NIHSS score, median (<i>IQR</i>)	3.00(2.00-4.00)	3.00(2.00-4.00)	0.051
ABCD2 score, median (<i>IQR</i>)	5.00(4.00-6.00)	5.00(5.00-6.00)	0.699

Stroke subtype			0.241
Large artery atherosclerosis	36(34.0)	38(32.2)	
Cardioembolism	20(18.9)	12(10.2)	
Small vessel occlusion	36(34.0)	48(40.7)	
Other/Undetermined etiology	14(13.2)	20(16.9)	
Infarct location			0.275
Anterior circulation	67(63.2)	67(56.8)	
Posterior circulation	38(35.8)	46(39.0)	
Both circulation	1(0.9)	5(4.2)	
Severity of responsible artery stenosis			0.093
normal	61(57.5)	82(36.6)	
Mild to moderate stenosis	6(5.7)	10(8.5)	
Severe stenosis	18(17.0)	14(11.9)	
occlusion	21(19.8)	12(10.2)	

*Values are presented as mean $\pm$ SD or $n(\%)$, unless indicated otherwise.

§Student t test or Mann-Whitney test was used for continuous values as appropriate and chi square test for categorical values.

Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); FPG, fasting plasma glucose; HDL-C high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; TC, total cholesterol; TG, total glyceride; and TIA, transient ischemic stroke.

Table 2. Univariate Analysis of Acute Mild Stroke Patients Stratified by Different Functional Outcomes

Variables*	Total (n=224)	mRS 0-1 (n=160)	mRS 2-6 (n=64)	Test values	P value§
Age, y, median (<i>IQR</i>)	66.00(59.00-74.00)	66.00(56.25-74.00)	65.00(61.25-74.00)	-1.129	0.259
Female	73(32.6)	41(25.6)	32(50.0)	12.363	0.001
Medical history					
Hypertension	160(71.4)	111(69.4)	49(76.6)	1.157	0.282
Diabetes mellitus	57(25.4)	31(19.4)	26(40.6)	10.881	0.001
Hyperlipoidemia	102(45.5)	69(43.1)	33(51.6)	1.312	0.252
Atrial Fibrillation	29(12.9)	23(14.4)	6(9.4)	1.014	0.314
Coronary heart disease	18(8.0)	15(9.4)	3(4.7)	1.359	0.244
Previous stroke/TIA	32(14.3)	25(15.6)	7(10.9)	0.820	0.365
Current smoking	78(34.8)	60(37.5)	18(28.1)	1.770	0.183
Medications prior to onset					
Antihypertension agents	129(57.6)	86(53.8)	43(67.2)	3.380	0.066
Antidiabetic agents	43(19.2)	25(15.6)	18(28.1)	4.605	0.032
Antiplatelet agents	25(11.2)	21(13.1)	4(6.3)	2.179	0.140
Anticoagulant agents	5(2.2)	3(1.9)	2(3.1)	0.005	0.943
Laboratory data, mmol/L					
FPG, median (<i>IQR</i>)	5.15(4.63-6.04)	5.02(4.57-5.83)	5.55(4.86-7.62)	-2.795	0.005
TC	4.34±0.91	4.25±0.90	4.57±0.90	2.437	0.016
LDL-C	2.54±0.76	2.48±0.76	2.68±0.75	1.772	0.078
HDL-C, median (<i>IQR</i>)	1.17(1.03-1.33)	1.16(1.02-1.30)	1.21(1.11-1.43)	-1.921	0.055
TG, median (<i>IQR</i>)	1.25(0.93-1.76)	1.29(0.96-1.68)	1.20(0.90-1.86)	-0.540	0.589
Admission blood pressure, mmHg					
Systolic blood pressure	151.33±20.14	150.88±20.55	152.44±19.20	0.552	0.603

Diastolic blood pressure	83.00(76.25-92.00)	85.00(77.00-94.00)	80.50(76.00-89.00)	-1.064	0.287
Baseline clinical profiles					
NIHSS score, median (<i>IQR</i>)	3.00(2.00-4.00)	3.00(2.00-3.75)	4.00(3.00-5.00)	-4.197	0.001
ABCD2 score, median (<i>IQR</i>)	5.00(5.00-6.00)	5.00(4.00-6.00)	6.00(5.00-6.00)	-3.258	0.001
Intravenous rt-PA treatment	106(47.3)	83(51.9)	23(35.9)	4.658	0.031
Stroke subtype				10.594	0.014
Large artery atherosclerosis	74(33.0)	43(26.9)	31(48.4)		
Cardioembolism	32(14.3)	27(16.9)	5(7.8)		
Small vessel occlusion	84(37.5)	65(40.6)	19(29.7)		
Other/Undetermined etiology	34(15.2)	25(15.6)	9(14.1)		
Infarct location				-	0.156
Anterior circulation	134(59.8)	90(56.3)	44(68.8)		
Posterior circulation	84(37.5)	66(41.3)	18(28.1)		
Both circulation	6(2.7)	4(2.5)	2(3.1)		
Severity of responsible artery stenosis				-	0.034
normal	143(63.8)	111(69.4)	32(50.0)		
Mild to moderate stenosis	16(7.1)	11(6.9)	5(7.8)		
Severe stenosis	32(14.3)	20(12.5)	12(18.8)		
occlusion	33(14.7)	18(11.3)	15(23.4)		
ICH	9(4.0)	4(2.5)	5(7.8)	2.110	0.146
sICH	1(0.4)	0(0.0)	1(1.6)	-	0.286

*Values are presented as mean $\pm$ SD or *n*(%), unless indicated otherwise.

§Student *t* test or Mann-Whitney *U* test was used for continuous values as appropriate and chi square test for categorical values.

Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); FPG, fasting plasma glucose; HDL-C high-density lipoprotein cholesterol; ICH, intracranial hemorrhage; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic ICH; TC, total cholesterol; TG, total glyceride; and TIA, transient ischemic stroke.

Table 3. Multivariable-adjusted Associations Between Covariates and Clinical Outcomes.

Outcomes	variables	OR (95%CI)	P values§
Excellent outcome ^a	Male	3.151 (1.577-6.293)	0.001
	Intravenous rt-PA	3.156 (1.526-6.528)	0.002
	Baseline NIHSS score, per 1 point	0.551 (0.413-0.735)	<0.001
	Severity of responsible artery stenosis	0.762 (0.619-0.938)	0.010
	FPG, per 1 mmol/L	0.824 (0.714-0.951)	0.008
Perfect Outcome ^b	Intravenous rt-PA	1.968 (1.084-3.573)	0.026
	Baseline NIHSS score, per 1 point	0.652 (0.512-0.831)	0.001
	Diabetes mellitus	0.355 (0.168-0.748)	0.006
	HDL-C, per 1 mmol/L	0.178 (0.050-0.627)	0.007
Significant improvement ^c	Male	6.182 (2.092-18.263)	0.001
	Intravenous rt-PA	2.448 (1.204-4.977)	0.013
	Baseline NIHSS score, per 1 point	0.740 (0.558-0.983)	0.038
END ^d	Severity of responsible artery stenosis	1.473 (1.134-1.914)	0.004
	Baseline ABCD2 score, per 1 point	2.293 (1.396-3.766)	0.001
	HDL-C, per 1 mmol/L	7.034 (1.217-40.674)	0.029
Any ICH ^e	Age, per 1 year	1.113 (1.020-1.215)	0.016
	Baseline NIHSS score, per 1 point	2.348 (1.168-4.721)	0.017
	Systolic blood pressure, per 1 mmHg	1.041 (1.002-1.080)	0.037
Recurrent ischemic stroke ^f	Male	0.227 (0.054-0.946)	0.042
	Both circulation infarction	20.778 (2.546-169.572)	0.005

§Multivariable binary logistic regression analysis was used.

aAdjusted for gender, intravenous rt-PA treatment, diabetes mellitus, antidiabetic agents, baseline NIHSS score, baseline ABCD2 score, stroke subtype, severity of responsible artery stenosis and laboratory data (FPG and TC). bAdjusted for intravenous rt-PA treatment, baseline NIHSS score, diabetes mellitus and laboratory data (FPG and HDL-C). cAdjusted for gender, intravenous rt-PA treatment and baseline NIHSS score. dAdjusted for diabetes mellitus, antidiabetic agents, baseline ABCD2 score, severity of responsible artery stenosis, laboratory data (FPG, TC and HDL-C) and intravenous rt-PA treatment. eAdjusted for age, baseline NIHSS score, admission systolic blood pressure and intravenous rt-PA treatment. fAdjusted for gender, infarct location (anterior circulation infarction as reference) and intravenous rt-PA treatment.

Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); CI, confidence interval; END, early neurological deterioration; FPG, fasting plasma glucose; HDL-C high-density lipoprotein cholesterol; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and rt-PA, recombinant tissue plasminogen activator.

Table 4. Efficacy of Baseline Scores for Predicting Adverse Prognosis

§ROC curves analysis was performed. aIndicator for predicting poor outcome at 90d with mRS of 2-6; bindicator for predicting END at 7d.

Independent variables	AUC (95% <i>CI</i>)	Cut-off values	Sensitivity	Specificity	<i>P</i> value§
Baseline NIHSS score ^a	0.675(0.594-0.756)	3.5	0.578	0.750	<0.001
Baseline ABCD2 score ^b	0.707(0.606-0.809)	4.5	0.692	0.641	0.001

Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); AUC, area under curve; CI, confidence interval; and NIHSS, National Institutes of Health Stroke Scale.

Figures

Figure 1

Comparisons of Clinical Outcomes with Mild Stroke Between Different Medical Approaches.

§Multivariable binary logistic regression analysis was used after adjusting for intravenous rt-PA treatment and variables with P <0.1 in univariate analysis for different outcomes. Abbreviations: CI, confidence interval; END, early neurological deterioration; ICH, intracranial hemorrhage; and OR, odds ratio.

Figure 2

Subgroup Analysis with Acute Mild Stroke for Excellent Outcome. §Multivariable binary logistic regression analysis was used. §Multivariable binary logistic regression analysis was used after adjusting for intravenous rt-PA treatment and variables with P <0.1 in univariate analysis for different outcomes. Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence

of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and rt-PA, recombinant tissue plasminogen activator.

Figure 3

Subgroup Analysis with Mild Stroke for Excellent Outcome. Abbreviations: ABCD2 score (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke); CI, confidence interval; and OR, odds ratio.