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# Effect of intravenous urokinase vs best medicine treatment on functional outcome for patients with acute minor stroke (TRUST): a randomized controlled trial

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## Abstract

**Background** The benefits of intravenous thrombolysis in patients with acute minor stroke remain controversial. For the aim of providing a better therapeutic strategy, high-quality trials are required to validate the efficacy of thrombolytic medicine other than intravenous recombinant tissue plasminogen and tenecteplase. In the trial, we evaluate the efficacy and safety of urokinase (UK) in acute minor stroke.

**Methods** This multicenter, open-label, blinded-endpoint, randomized controlled clinical trial enrolled patients with minor stroke within 6 h of symptom onset, with a NIHSS score ≤ 5. The trial was conducted at 25 hospitals in China between October 2020 and February 2023. Eligible patients were randomized to the UK group (1,000,000 U) or the best medicine treatment group. The responsible investigator recommended and implemented the best medicine treatment based on guidelines. The primary endpoint was an excellent functional outcome, defined as a modified Rankin scale (mRS) score of 0–1 at 90 days. The primary safety outcome was symptomatic intracranial hemorrhage (sICH) within 36 h.

**Results** A total of 999 patients were enrolled in the trial, the median age was 64 years, 371 (36.9%) were women; the median (IQR) NIHSS score was 3 (2–4). At 90 days, the primary endpoint was observed in 427 patients (84.9%) in the UK group and 425 patients (85.7%) in the control group (adjusted risk ratio [RR] 1.00, 95% CI 0.96–1.05, $p = 0.87$). A total of 3 patients in the UK-treated (0.6%) group experienced sICH compared to 1 patient (0.2%) in the control group (RR 1.83, 95% CI 0.16–20.27, $p = 0.62$).

**Conclusions** For patients with acute minor stroke treated within 6 h of symptom onset, UK intravenous thrombolysis treatment was not found to be beneficial in terms of excellent functional outcome at 90 days, whereas it was safe.

**Trial registration** ClinicalTrials.gov Identifier: NCT04420351.

**Keywords** Minor stroke, Intravenous thrombolysis, Urokinase, Antiplatelet therapy, Function outcome

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## Background

Minor stroke constitutes roughly half of patients with acute ischemic stroke, but not all minor stroke patients have favorable outcomes [1]. Approximately 15% of patients experience early neurological deterioration, and some patients may experience death or disability at the 90-day follow-up without intravenous thrombolysis [2–4]. However, the benefits of recombinant tissue plasminogen activator (rt-PA) and tenecteplase thrombolytic remain controversial compared to antiplatelet therapy in minor stroke. As reported in several representative studies, the PRISMS trial indicated that alteplase did not improve the proportion of favorable functional outcomes at 90 days compared with aspirin for minor stroke, however, the trial was prematurely terminated by the sponsor, due to insufficient patient enrollment [5]. The ARAMIS study also did not demonstrate the superiority of intravenous alteplase over clopidogrel plus aspirin in patients with minor non-disabling acute ischemic stroke [6]. Furthermore, the TEMPO-2 trial failed to show that tenecteplase outperformed the non-thrombolytic standard of care in patients with acute minor stroke and intracranial occlusion [7]. However, the AHA/ASA [8] and ESO [9] guidelines recommend intravenous thrombolysis in patients with disabling minor stroke, although the evidence level is relatively low. The Chinese guideline [10] has no clear statement of intravenous thrombolysis for disabling minor stroke and addresses non-disabling minor stroke as a relative contraindication. Based on these controversies, further exploration is imperative. Urokinase (UK), extensively utilized in China, is recommended in the latest Chinese stroke guidelines for patients with acute ischemic stroke of intravenous thrombolytic therapy administered within 6 h of symptom onset [11–14]. Registry studies indicate that UK and other thrombolytic agents exhibit comparable effectiveness and safety profiles in acute ischemic stroke patients [15, 16]. Thus, UK may serve as a candidate thrombolytic medicine for minor stroke patients. However, the efficacy and safety of UK in minor stroke patients are still uncertain.

The ThRombolysis of Urokinase for minor STroke Trial (TRUST) was conducted to evaluate the efficacy and safety of intravenous UK for acute minor stroke treatment.

## Methods

### Study design and participants

The TRUST trial was a prospective, open-label, randomized, blinded-endpoint, and multicenter study aimed at assessing the efficacy and safety of intravenous UK administered within 6 h of symptom onset, in accordance with Chinese stroke guidelines [11]. The rationale, design, and methods of the trial have been described previously [17], in addition, the initial and final protocols were shown in the Additional File1 The protocol received approval from the ethics committees of the First Affiliated Hospital of Zhengzhou University and of all participating sites. The study was conducted at 25 hospitals (Additional File 2: Table S1) in China from October 4, 2020, to November 11, 2022. Patients or their representatives provided informed consent before enrollment.

Patients were eligible if they had an acute ischemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score of 0–5, age 18–80 years, treatment initiation within 6 h of symptom onset, first stroke occurrence, or patients with previous stroke of a pre-stroke modified Rankin scale (mRS) score $\leq 1$. Head computed tomography (CT) imaging or magnetic resonance imaging (MRI) was required, for patients with suspected clinical neurologic events. Patients with lesions larger than 1/3 middle cerebral artery territory, intracranial hemorrhage, complications, or other contraindications were excluded. We enrolled all ischemic stroke patients with NIHSS $\leq 5$ without distinguishing disabling and non-disabling in present research. Considering that there is a certain subjectivity of patients and clinical physicians in evaluating disabling and non-disabling. The protocol provides further details on the inclusion and exclusion criteria [17].

### Randomization

Randomization sequences were generated by an independent statistician using a permuted block randomization schema with a block size of 4 stratified by center. Patients were randomly assigned in a 1:1 ratio to receive either UK intravenous thrombolysis or guideline-based best medicine treatment by a web-based randomization system.

### Treatment

The intravenous thrombolysis group was administered 1,000,000 U UK dissolved in 100 mL of saline via continuous intravenous infusion for 30 min, and the treatment was given within 6 h of stroke onset. The guideline-based best medicine treatment group received antithrombotic treatments, as implemented by the local investigator. The best medication treatment was initiated immediately after randomization. Post-treatment clinical management followed established protocols and clinical guidelines [17]. The study required follow-up neuroimaging (CT imaging or MRI as per institutional standard of care) within 22 to 36 h post-randomization.

### Outcomes

The primary outcome was an excellent functional outcome, defined as the mRS score of 0–1 at 90 days. The secondary efficacy outcomes included new clinical vascular event (vascular death, hemorrhagic stroke, ischemic stroke, or myocardial infarction), functional disability (assessed by the 6-level ordinal mRS score, combining levels 5 and 6), general health-related quality of life (EuroQoL group EQ-5D) score, range: 0 (death) to 1 (perfect health), and Barthel Index score ≥ 95 (range: 0 [totally dependent] to 100 [independent]) at 90 days.

The primary safety outcome was symptomatic intracranial hemorrhage (sICH) within 36 h post-randomization, based on the definition of the National Institute of Neurological Disorders and Stroke (NINDS) criteria: clinical progression accompanied by the imaging evidence of intracranial hemorrhage within 36 h of intravenous thrombolysis [18]. Additional safety endpoints included 90-day all-cause mortality, adverse events, and severe adverse events. A blinded central adjudication committee confirmed all reported efficacy and safety endpoints.

### Statistical analysis

We estimated the proportion of the primary efficacy outcome based on the findings from the Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) study [19]. The primary outcome was estimated at 81.5% for the control group and 88% for the UK group. To detect a 6.5% difference in the primary outcome between the intervention and control group with 80% power and a two-sided alpha of 0.05, accounting for a 5% loss to follow-up, 1002 subjects were required.

Independent academic statisticians analyzed the trial according to the statistical analysis plan and the protocol detailed in Supplement 1. The primary endpoint analysis was conducted on the intention-to-treat population using a generalized linear model (GLM), adjusting for pre-specified covariates: age, gender, baseline NIHSS score, systolic blood pressure, and myocardial infarction. Adjusted odds ratios (ORs), risk ratios (RRs), and their 95% confidence intervals (CIs) were derived from logistic regression and log-binomial regression models, respectively. To evaluate the impact of crossovers between the intervention and control group, we analyzed both the per-protocol population (patients treated according to the randomization assignment [excluding crossovers] and did not violate the inclusion or exclusion criteria or had significant protocol deviations) and the as-treated population (based on the actual treatment received during the study, regardless of the initially assigned randomized treatment). Additionally, results from treating assignment as an instrumental variable were reported as sensitivity analyses to handle the effect of treatment-switching in this study. The secondary binary outcomes were analyzed using the GLM model, as done for the primary endpoint analysis. For the analysis of the ordinal mRS score at 90 days, an ordinal logistic regression model was utilized to calculate common OR and 95% CI. The GLM with a normal distribution and identity link function was employed to estimate the adjusted mean difference and 95% CI for secondary continuous outcomes.

Subgroup analyses were conducted based on age (< 65 or ≥ 65 years), gender (women or men), the time from symptom onset to treatment (≤ 4.5 or > 4.5 h), IIb/IIIa inhibitors prescription (yes or no), the history of hypertension, diabetes mellitus, dyslipidemia, and prior use of antiplatelet or anticoagulant medication (yes or no). The interaction term between the subgroup variable and treatment group in the model was used to assess the homogeneity of the treatment effect.

Given the risk of type I error inflation from multiple comparisons, the subgroup and secondary outcome analysis findings should be considered exploratory. All data analyses were conducted using SAS (version 9.4). Two-sided $p$ values less than 0.05 were deemed statistically significant.

## Results

### Trial patients

Between Oct 4, 2020, and Nov 11, 2022, 1005 patients with stroke were screened in the study across 25 medical centers in China. The trial was completed on February 20, 2023. Six patients were deemed ineligible based on exclusion criteria. Thus, the remaining 999 patients were randomly assigned either to the UK group (503 patients) or the control group (496 patients). Of these, 177 patients had a protocol violation: 114 (23.0%) patients in the control group crossed over to the UK group, and 63 (12.5%) patients in the UK group crossed over to the control group. The per-protocol population patients included 802 patients (429 in the UK group and 373 in the control group), while the as-treated population comprised 979 patients (543 in the UK group and 436 in the control group). Study randomization and enrollment are shown in Fig. 1.

### Patients characteristics

Patients' baseline characteristics are presented in Table 1. Baseline characteristics were generally balanced between treatment groups in the intention-to-treatment (ITT) population, except for systolic blood pressure (152 mmHg vs. 149 mmHg), myocardial infarction (4.0% vs. 1.7%), and baseline NIHSS score (3 vs. 2). Baseline characteristics of the per-population and

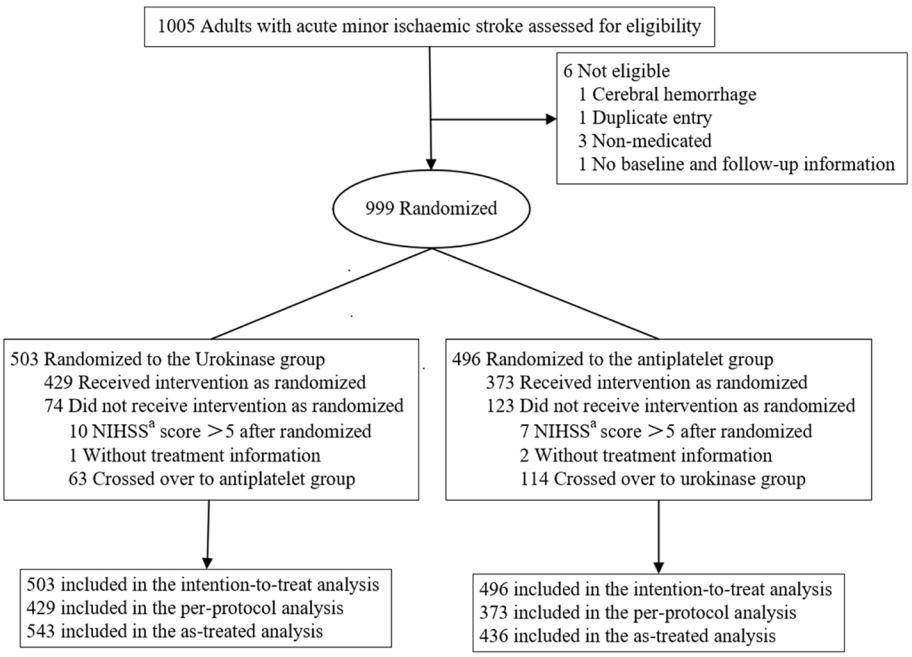


**Fig. 1** Patient flow in the TRUST randomized clinical trial. [a]NIHSS indicates National Institutes of Health Store Scale scores

**Table 1** Baseline characteristics of patients in the intention-to-treatment population

| Baseline characteristics | Urokinase *n* = 503 | Control *n* = 496 |
|---|---|---|
| Age, years, mean ± SD | 62.7 ± 10.7 | 63.1 ± 10.7 |
| Female, No. (%) | 186 (37.0) | 185 (37.3) |
| BMI,kg/m$^2$, mean ± SD | 24.5 ± 3.3 | 24.2 ± 3.3 |
| Current smoking[a], No. (%) | 192 (38.2) | 178 (35.9) |
| Current drinking[b], No. (%) | 167 (33.2) | 141 (28.4) |
| Medical history | | |
| Hypertension, No. (%) | 272 (54.1) | 253 (51.0) |
| Diabetes mellitus, No. (%) | 75 (14.9) | 72 (14.5) |
| Dyslipidemia, No. (%) | 9 (1.8) | 16 (3.2) |
| Previous stroke[c], No. (%) | 151 (30.0) | 137 (27.6) |
| Myocardial infarction, No. (%) | 20 (4.0) | 7 (1.4) |
| Arrhythmias, No. (%) | 20 (4.0) | 20 (4.0) |
| Valvular heart disease, No. (%) | 2 (0.4) | 0 (0.0) |
| Peripheral arterial disease, No. (%) | 2 (0.4) | 2 (0.4) |
| Systolic blood pressure at randomization, mmHg, mean ± SD | 152.7 ± 21.9 | 149.9 ± 21.6 |
| diastolic blood pressure at randomization, mmHg, mean ± SD | 88.0 ± 13.0 | 88.4 ± 13.2 |
| Onset-to-treatment, h, No. (%) | | |
| < 4.5 h | 352 (70.0) | 337 (67.9) |
| ≥ 4.5 h | 151 (30.0) | 159 (32.1) |
| Door-to-needle (IQR), h | 0.6 (0.3–1.0) | 0.6 (0.3–1.1) |
| Baseline NIHSS score (IQR) | 3.0 (2.0–4.0) | 2.0 (1.0–4.0) |

*Abbreviations*: *SD* standard deviation, *BMI* body mass index, *IQR* interquartile range, *NIHSS* National Institutes of Health Stroke Scale

[a] Current smoking defined as consuming at least 1 cigarette per day within 1 year before the onset of the disease

[b] Current drinking defined as consuming alcohol at least once a week within 1 year before the onset of the stroke and consume alcohol continuously for more than 1 year

[c] Referring to patients with premorbid modified Rankin scale (mRS) score ≤ 1

as-treated population are shown in the Additional File 2: Table S3–S4.

### Efficacy outcomes

In the ITT population, the primary endpoint analysis showed no significant differences in the proportion of patients achieving an excellent functional outcome (mRS 0–1) at 90 days between the intervention group (427/503, 84.9%) and the control group (425/496, 85.7%, adjusted RR 1.00, 95% CI 0.96–1.05, $p=0.87$; Table 2). The per-protocol and as-treated analyses yielded comparable results (Additional File2: Table S5–S6). Comparable findings were also observed using instrumental variable analyses to handle treatment crossovers (Additional File2: Table S7–S8). No significant differences in the excellent functional outcome between disabling and non-disabling patients, as shown in Additional File2: Table S9. Subgroup analyses indicated that the treatment effect may differ based on age, diabetes status, and previous antithrombotic use.

The occurrence rates of secondary outcomes were similar between the intervention and control groups in the ITT population. No significant difference was observed in the proportion of patients with new vascular events

**Table 2** Efficacy and safety outcomes in the intention-to-treatment population

| Outcome | No. (%) | | Effect measure | Treatment effect (95% CI)[a] | *P* value |
|---|---|---|---|---|---|
| | Urokinase (*n* = 503) | Antiplatelet (*n* = 496) | | | |
| **Primary efficacy outcome** | | | | | |
| mRS score[b] 0–1 at 90 days | 427 (84.9) | 425 (85.7) | Risk ratio | 1.00 (0.96 to 1.05) | 0.87 |
| | | | Odds ratio | 1.06 (0.73 to 1.53) | 0.76 |
| **Secondary efficacy outcome**s | | | | | |
| New vascular events within 90 days | 33 (6.6) | 37 (7.5) | Risk ratio | 0.91 (0.58 to 1.44) | 0.68 |
| | | | Odds ratio | 0.91 (0.55 to 1.49) | 0.70 |
| Shift mRS | | | Common odds ratio | 1.22 (0.95 to 1.55) | 0.12 |
| 0 | 271 (53.9) | 253 (51.0) | | | |
| 1 | 156 (31.0) | 172 (34.7) | | | |
| 2 | 43 (8.5) | 29 (5.8) | | | |
| 3 | 18 (3.6) | 17 (3.4) | | | |
| 4 | 7 (1.4) | 8 (1.6) | | | |
| 5 | 1 (0.2) | 4 (0.8) | | | |
| 6 | 7 (1.4) | 13 (2.6) | | | |
| Barthel Index ≥ 95 at 90 days | 280 (56.2) | 279 (57.4) | Risk ratio | 1.01 (0.94 to 1.09) | 0.72 |
| | | | Odds ratio | 1.08 (0.83 to 1.40) | 0.58 |
| EQ-5D[c] score at 90, mean ± SD | 85.5 ± 22.4 | 86.4 ± 20.8 | Mean difference | −0.20 (−2.90 to 2.49) | 0.88 |
| **Safety Outcomes** | | | | | |
| sICH[d] within 36 h | 3 (0.6) | 1 (0.2) | Risk ratio | 1.83 (0.16 to 20.27) | 0.62 |
| | | | Odds ratio | 1.85 (0.17 to 20.77) | 0.62 |
| Overall mortality within 90 days | 7 (1.4) | 13 (2.6) | Risk ratio | 0.52 (0.21 to 1.33) | 0.18 |
| | | | Odds ratio | 0.50 (0.19 to 1.29) | 0.15 |
| Adverse events | 70 (13.9) | 71 (14.3) | Risk ratio | 0.97 (0.71 to 1.32) | 0.84 |
| | | | Odds ratio | 0.97 (0.67 to 1.39) | 0.86 |
| Serious adverse events | 18 (3.6) | 28 (5.6) | Risk ratio | 0.61 (0.34 to 1.10) | 0.10 |
| | | | Odds ratio | 0.61 (0.33 to 1.13) | 0.12 |

*Abbreviations*: *mRS* modified Rankin scale, *SD* standard deviation, *sICH* symptomatic intracranial hemorrhage, *AE* adverse events, *SAE* serious adverse events

[a] Treatment effects for the urokinase group as compared with the antiplatelet group were adjusted for age, gender, systolic blood pressure, baseline National Institutes of Health Stroke Scale (NIHSS) score, and myocardial infarction

[b] Modified Rankin scale (mRS) scores range from 0 to 6. 0, no symptoms; 1, symptom without significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death

[c] Total scores on the EuroQol 5-Dimension questionnaire (EQ-5D) range from 0 to 100, with higher scores indicating a better quality of life across the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression

[d] Symptomatic intracerebral hemorrhage (sICH) was defined by National Institute of Neurological Disorders and Stroke (NINDS) criteria: clinical findings of progression plus imaging evidence of hemorrhage within 36 h of thrombolysis, or deterioration in NIHSS score of ≥ 4 with a radiological parenchymal hemorrhage type 2

at 90 days (33 [6.6%] of 503 patients in the intervention group vs. 37 [7.5%] of 496 patients in the best medicine treatment group, adjusted RR 0.91, 95% CI 0.58–1.44, $p=0.68$). Similarly, the ordinal analysis of mRS scores showed no significant difference (adjusted OR 1.22, 95% CI 0.95–1.55, $p=0.12$; Table 2, Fig. 2). Comparable outcomes were observed in both the per-protocol and as-treated analyses (Additional File2: Table S5–S6). We used different methods to correct for the potential bias caused by cross-over, and the results remained unchanged (Additional File2: Table S7–S8). And there was no statistically significant difference in the primary outcome between disabling and non-disabling patients (Additional File2: Table S9) (Fig. 3).

### Safety outcomes

The intervention group exhibited a higher, though not statistically significant, rate of sICH within 36 h of post-randomization compared to that in the control group (0.6% vs. 0.2%; adjusted RR 1.83, 95% CI 0.16–20.27, $p=0.62$; Table 2). Mortality rates were 1.4% (7 patients) in the UK group and 2.6% (13 patients) in the control group. The proportion of patients experiencing adverse events was comparable between the UK group (13.9%) and the control group (14.3%), as were the rates of serious adverse events (3.6% in the UK group and 5.6% in the control group).

## Discussion

The TRUST trial did not demonstrate any benefit of intravenous thrombolysis with 1,000,000 U UK over guideline-based best medicine treatment for patients with acute minor ischemic stroke. UK intravenous thrombolysis did not elevate the risk of sICH compared to guideline-based best medicine treatment.

The findings align with previous trials on intravenous thrombolysis in patients with minor stroke [20]. The PRISMS study, the inaugural randomized multicenter trial comparing rt-PA and single antiplatelet therapy for acute nondisabling minor stroke, found no significant difference in 90-day functional outcomes between the two groups [5]. The ARAMIS trial indicated that dual antiplatelet therapy is as effective as intravenous alteplase for achieving excellent functional outcomes at 90 days in patients with minor nondisabling acute ischemic stroke treated within 4.5 h [6]. Similarly, The TEMPO-2 trial found that intravenous tenecteplase did not benefit patients with minor stroke and focal perfusion abnormality or intracranial occlusion [7]. Our trial also found that intravenous UK did not improve functional outcomes in patients with minor stroke. In the TRUST trial, the proportion of patients with excellent functional outcomes (84.9% in the UK group vs. 85.7% in the control group) was lower than that achieved in the ARAMIS study (91.5% vs 93.7%) [6], but was comparable to the PRISMS trial (78.2% vs 81.5%). It is worth noting that the ARAMIS study excluded patients with potential cardioembolic conditions, but identifying cardioembolic development during the brief hyperacute phase may be challenging. The TEMPO-2 trial enrolled minor stroke patients with imaging evidence of intracranial occlusion or focal perfusion lesion, which may prolong the door-to-needle time. The TRUST trial included all patients with NIHSS score $\leq 5$, without distinguishing between disabling and nondisabling individuals. Compared to the aspirin monotherapy group in PRISMS, the antiplatelet group of the TRUST trial predominantly used dual

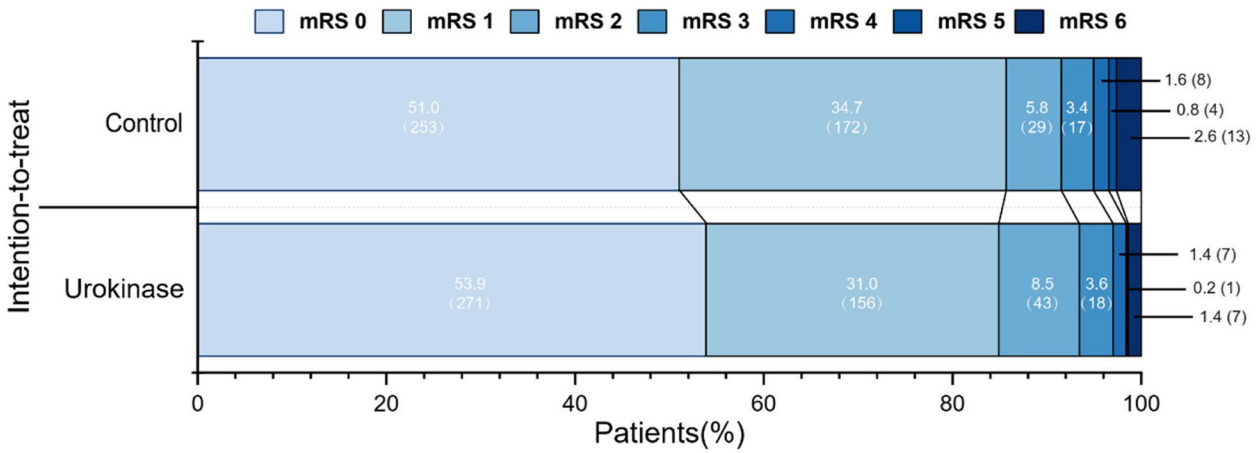


**Fig. 2** Distribution of modified Rankin scale (mRS) scores at 90 days in the intention-to-treat population. The mRS scores ranged from 0 to 6: 0, no symptoms; 1, symptom without clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death

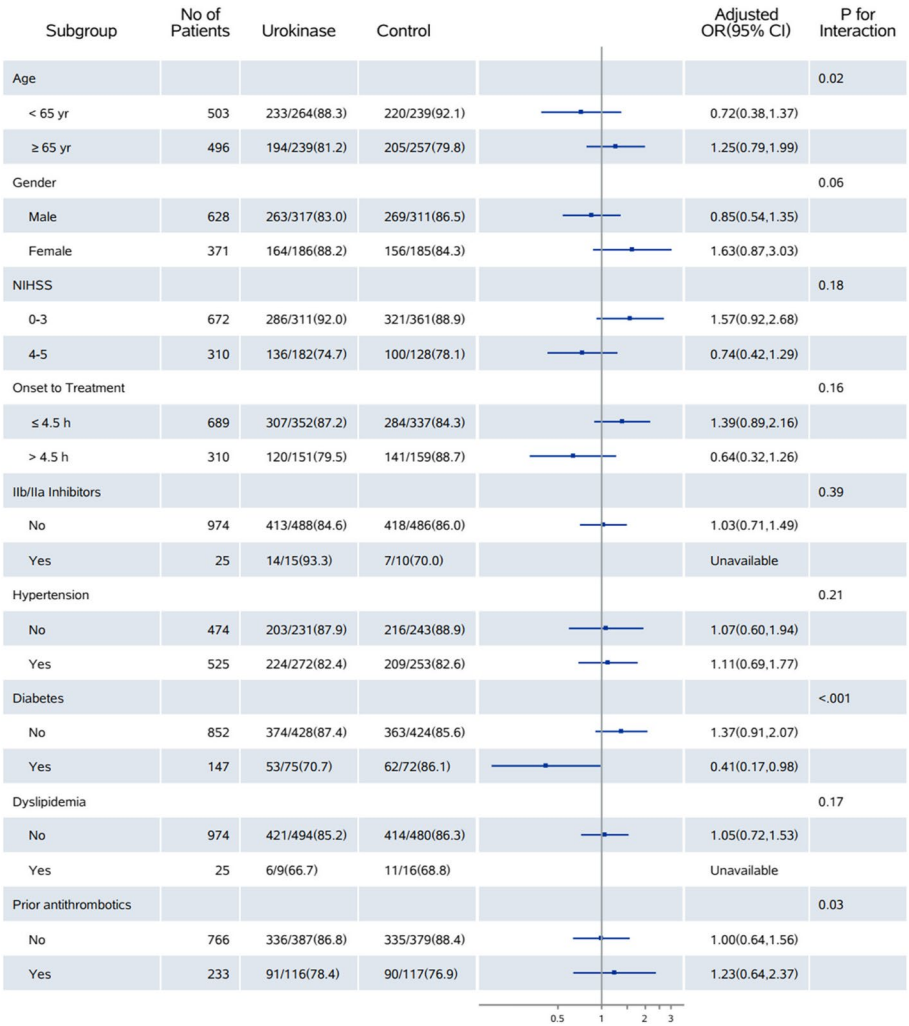


**Fig. 3** Primary outcome by prespecified subgroups in the intention-to-treat population

antiplatelet therapy, which may have slightly improved the functional outcome. The results from the CHANCE sub study showed that clopidogrel plus aspirin improved the 90-day functional outcome compared to that with aspirin alone [21].

Our trial had several limitations: (1) A high crossover rate (23.8%) was observed, which may have compromised the integrity of the trial. However, the consistency of the per-protocol, as-treated, and instrumental analyses with the primary analysis indicates the robustness of the findings; (2) There were some imbalances in some baseline variables, such as NIHSS sore, which may confound our results. Nevertheless, the primary analysis was adjusted for these baseline imbalances, minimizing potential confounding bias; (3) Although the trial was open-label, which could introduce bias from investigators and subjects, blinded endpoint evaluations were employed to mitigate bias in the primary outcomes; (4) To our knowledge, no study has suggested a specific dosage of UK based on body weight, therefore, we used the minimum dosage suggested by guidelines, which may result in insufficient UK dosage and impact the outcomes. Further research is needed to determine dose-dependent effectiveness of higher doses of UK. (5) Although the trial was multi-center, based on geographic and population limitations, the enrolled patients were lack of ethnic diversity. The findings may need further verification in other populations.

## Conclusions

For patients presenting with acute minor stroke (NIHSS ≤ 5) within 6 h of symptom onset, there is no evidence to support that low-dose UK intravenous thrombolysis increases the likelihood of an excellent functional outcome at 90 days compared to best medicine treatment.

**Abbreviations**

| | |
|---|---|
| ARAMIS | Antiplatelet vs rt-PA for Acute Mild Ischemic Stroke |
| CHANCE | Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events |
| CT | Computed tomography |
| ITT | Intention-to-treatment |
| GLM | Generalized linear model |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin scale |
| NIHSS | National Institutes of Health Stroke Scale |
| OR | Odds ratio |
| POINT | Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA |
| PRISMS | Rt-PA for Ischemic Stroke with Mild Symptoms trial |
| rt-PA | Recombinant tissue plasminogen activator |
| sICH | Symptomatic intracranial hemorrhage |
| TEMPO-2 | Tenecteplase Versus Standard of Care for Minor IschAemic Stroke with Proven Occlusion |
| TRUST | Thrombolysis of Urokinase for Mild Stroke |
| UK | Urokinase |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03820-2.

Additional file 1. The Initial Protocol, the Final Protocol, Detail of Protocol Change and the Statistical Analysis Plan.

Additional file 2. Steering Committee, Executive Committee, Data Monitoring and Safety Board, Clinical Events Adjudication Committee, Biostatisticians, and Table 1 -S9. Table 1. Recruitment by Site in TRUST Trial; Table 2. Inclusion and Exclusion Criteria; TableS3-S4. Baseline Characteristics of Patients in the per-protocol and As-treated population; TableS5-S6. Efficacy and Safety Outcomes in the per-protocol and As-treated population; TableS7-S8. Analyzing Primary Efficacy Outcome Using Different Methods; TableS9. Analyzing Primary Efficacy Outcome in Disabling and Non-disabling Population.

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**Authors' contributions**
YLT, BS, YMX, QD, XC, FSB, JY, and HQG contributed to study design, data interpretation, and writing and revising the manuscript. YG, LZ, KL, YFX, and RZ contributed to study design and interpreted the data. JW, LLP, HF, XSH, HLG, BGX, JLL, and YQL contributed to trial participation, enrolment of patients and follow-up of patients. XW, CYJ, and KJD contributed to data collection, data analysis, figures, and tables. DLW and MMN contributed to supervise the trial process. All authors read and approved the final manuscript. The drafts of the manuscript were written by the first and last authors, all authors provided suggestions and with no external writing assistance.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The trial was approved by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University (SS-2019-034) and of each participating site. Patients or their representatives provided informed consent before enrollment.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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