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Prourokinase vs Standard Care for Patients With Mild Ischemic Stroke
The PUMICE Randomized Clinical Trial

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IMPORTANCE Trials have not demonstrated superiority of alteplase or tenecteplase vs standard care in patients with mild stroke and have raised safety concerns. Prourokinase is an alternative fibrinolytic that may have a favorable safety profile, and the benefit-risk profile of prourokinase in mild stroke is unknown.

OBJECTIVE To investigate the efficacy and safety of prourokinase in mild ischemic stroke within 4.5 hours of symptom onset.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, prospective, open-label, blinded–end point randomized clinical trial conducted from November 2022 through December 2023 with 3 months of follow-up. The trial was conducted at 89 hospitals in China. Patients with a baseline National Institutes of Health Stroke Scale score of 5 or less (scores range from 0-42, with higher scores indicating more severe neurological deficit) within 4.5 hours from the time the patient was last known to be well. Patients with intention to proceed to endovascular treatment were excluded.

INTERVENTIONS Eligible patients were randomly assigned in a 1:1 ratio to receive prourokinase, 35 mg (15-mg bolus + 20-mg infusion over 30 minutes) or standard care, including antiplatelet or anticoagulant therapy, at the discretion of local investigators.

MAIN OUTCOMES AND MEASURES The primary outcome was modified Rankin Scale score of 0 or 1 (range, 0-6, with higher scores indicating greater disability) at day 90. Safety outcomes were symptomatic intracranial hemorrhage and death.

RESULTS Of 3836 patients who underwent screening, 1446 (37.7%) were enrolled in the trial. Median (IQR) age was 65.9 (57.7-72.7) years, and 948 were male (65.5%). A total of 723 patients were assigned to prourokinase and 723 to standard care. The primary outcome occurred in 639 patients (88.5%) in the prourokinase group and 658 (91.0%) in the standard care group (relative risk, 0.97; 95% CI, 0.94-1.01; 2-sided $P = .12$). Symptomatic intracranial hemorrhage was 0.7% (5 of 723 patients) with prourokinase and 0% with standard care, and mortality at 90 days was 2.3% and 1.4%, respectively.

CONCLUSIONS AND RELEVANCE Results of this randomized clinical trial demonstrate that prourokinase was not superior to standard care to improve the functional outcomes for patients with mild ischemic stroke within 4.5 hours after symptom onset but had a similar safety profile.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05507645

Visual Abstract

Supplemental content

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Group Information: A list of the PUMICE Investigators appears in Supplement 4.

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Approximately one-half of patients with ischemic stroke present with mild neurological deficits, as defined by a National Institutes of Health Stroke Scale (NIHSS) score of 5 or less.[1] Up to 15% of patients with initially mild stroke may experience early worsening of signs and symptoms.[2] At 90 days, approximately 15% of patients with mild stroke are disabled, and 4% have died.[3,4]

Post hoc analysis of trials suggest a therapeutic benefit of intravenous thrombolysis in patients with mild ischemic stroke, presumably most of whom had disabling deficits based on trial eligibility criteria.[5,6] However, 2 phase 3 randomized clinical trials, The Potential of r-tPA for Ischemic Strokes With Mild Symptoms (PRISMS) and Antiplatelet vs r-tPA for Acute Mild Ischemic Stroke (ARAMIS), that enrolled patients with nondisabling mild stroke by different definitions found that intravenous alteplase had no benefit over antiplatelet agents and numerically increased the risk of bleeding.[7,8] The recently published Tenecteplase vs Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO-2) trial included patients with mild stroke and evidence of vessel occlusion or focal perfusion abnormality. The TEMPO-2 trial demonstrated no benefit, and potentially increased mortality, with intravenous tenecteplase treatment.[9] In this context, although guidelines include recommendations for thrombolytics in mild but disabling stroke,[10,11] no individual trial in patients with mild stroke has demonstrated benefit. Furthermore, the differentiation of disabling from nondisabling deficits is challenging to operationalize in the context of emergency assessment.

Prourokinase, as a specific plasminogen activator, has the potential advantage of lower bleeding risk[12] and has been proven to be beneficial in intra-arterial thrombolysis for patients with stroke.[13] A recent trial[14] demonstrated that intravenous prourokinase, 35 mg, in patients with moderate and severe stroke within 4.5 hours of symptom onset was noninferior to alteplase, with a favorable safety profile. Whether prourokinase benefits mild stroke is unknown; therefore, we aimed to conduct the Prourokinase for Mild Ischemic Cerebrovascular Events (PUMICE) trial to investigate the efficacy and safety of prourokinase in mild ischemic stroke (NIHSS score ≤5) within 4.5 hours of symptom onset.

Key Points

Question Does intravenous prourokinase benefit patients with ischemic stroke presenting with minor neurologic deficits?

Findings In this randomized clinical trial that included 1446 patients with acute ischemic stroke, there was no significant difference in excellent functional outcome at 90 days between those treated with prourokinase vs standard care.

Meaning Results demonstrate that prourokinase was not superior to standard care for the treatment of patients with mild ischemic stroke within 4.5 hours after symptom onset.

Methods

Study Design

The PUMICE trial was a multicenter, prospective, open-label, blinded-end point randomized clinical trial of prourokinase compared with standard care in acute mild ischemic stroke (NIHSS score ≤5) within 4.5 hours after symptom onset. Ethical approval for the trial was granted by the institutional review board at Beijing Tiantan Hospital and all participating sites. The protocol was published[15] and approved by the ethics committees of all participating sites. The final protocol (Supplement 1) and statistical analysis plan (Supplement 2) were completed on August 7, 2023, and March 28, 2024, respectively. The trial was conducted at 89 hospitals (eAppendix 1 in Supplement 3) in China. Written informed consent was provided by all participants or their authorized representatives. The trial was designed and supervised by a steering committee and conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for good clinical practice. An independent data and safety monitoring committee periodically assessed safety data (eAppendix 2 in Supplement 3). An independent clinical research organization (ARO-NS Beijing Technology Ltd) monitored the trial for quality control. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Patients were eligible for inclusion if they had an ischemic stroke onset within 4.5 hours of enrollment, a premorbid modified Rankin Scale (mRS) score no more than 1 (scores range from 0-6, with higher scores indicating greater disability), and a baseline NIHSS score of 5 or less (scores range from 0-42, with higher scores indicating more severe neurological deficit). Patient ethnic group was self-reported and verified by identification card and included the following: Han, Hui, Man, Miao, Zhuang, Miao, and other ethnicity. China is a multiethnic country with varying genetics; therefore, we collected this information at baseline. Exclusion criteria were physician intention to proceed to endovascular treatment (which is not recommended in guidelines with an NIHSS score <6) and patients who had guideline-based contraindications to thrombolytics. Whether symptoms were regarded as disabling or not was not part of trial eligibility. Additional information about inclusion and exclusion criteria is provided in eAppendix 3 and 4 in Supplement 3, respectively. Baseline stroke severity (NIHSS score) and premorbid mRS score were evaluated by trained and certified physicians.

Randomization and Masking

Eligible participants were randomized in a 1:1 ratio to receive intravenous prourokinase or standard care. A central randomization system automatically generated the randomization sequence using a simple randomization method.

The intravenous thrombolytic treatment was open label. Evaluators for clinical assessments of primary and secondary efficacy outcomes and the independent clinical-event adjudication committee for reviewing adverse events and serious adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, remained blinded to treatment allocation.

Interventions

Intravenous prourokinase was administered at a total dose of 35 mg, with 15 mg given as an intravenous bolus over 3 minutes and the remaining dose administered via intravenous infusion over 30 minutes. Standard care, including antiplatelet or anticoagulant therapy at the discretion of local investigators, followed the 2018 Chinese guidelines for acute ischemic stroke diagnosis and treatment.[16]

Outcomes

The primary outcome was the proportion of patients with no disability, defined as an mRS score of 1 or less at 90 days. Secondary outcomes were functional improvement by 1 or more mRS categories (ordinal distribution of mRS score at 90 days), functional independence (proportion of mRS score ≤2 at 90 days), early neurological improvement (a decrease in NIHSS score of at least 4 points compared with baseline or NIHSS score ≤1 point at 24 hours), the proportion of Barthel Index score of 75 to 100 points at 90 days (scores range from 0 to 100, with higher scores indicating greater independence), quality of life at 90 days (EuroQoL 5-Dimension 5-Level Questionnaire [EQ-5D-5L]; scores range from 0-100, with higher scores indicating better quality of life), and activities of daily living at 90 days (Lawton Instrumental Activity of Daily Living [IADL]; scores range from 0-100, with higher scores indicating greater independence in activities of daily living).

Safety outcomes were the incidence of symptomatic intracranial hemorrhage within 36 hours (as defined by the European Cooperative Acute Stroke Study III; any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration),[17] the rate of mortality at 90 days, the incidence of moderate and severe systemic bleeding at 90 days (as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria),[18] and adverse events and serious adverse events at 90 days. Definitions of outcomes are included in eAppendix 5 in Supplement 3.

Brain computed tomography (CT) was used for screening before randomization, the Alberta Stroke Program Early CT Score (ASPECTS) was used to assess the infarct size, and repeated brain CT at 24 hours after randomization was used to detect hemorrhagic transformation before antithrombotic management decisions. Repeated CT within 36 hours was performed to identify symptomatic intracranial hemorrhage in patients who had symptoms or signs of deterioration. Clinical assessments (including neurological examination, laboratory tests, medications, and imaging data) were conducted at each site within 24 hours, 36 hours, 7 days or before discharge, and 90 days by trained and certified evaluators who were unaware of the trial group assignments. The mRS, EQ-5D-5L, Barthel Index, and IADL scores at 90 days were assessed face to face or by telephone.

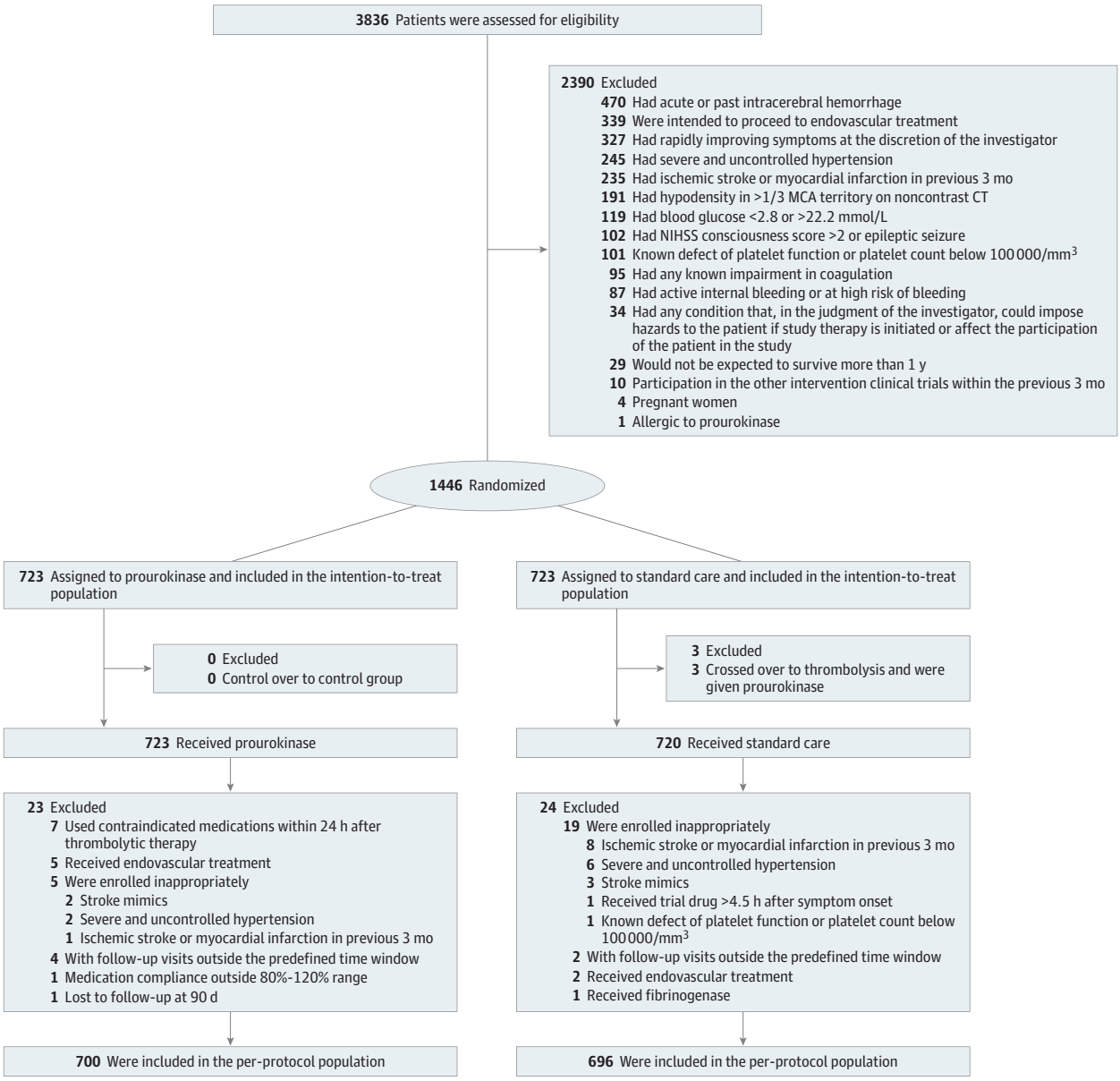
Sample Size Calculation

At the time of the study design, there were limited data on 90-day mRS scores for patients with mild ischemic stroke within 4.5 hours of onset in the Chinese population. The proportion of patients with mild stroke (NIHSS score ≤5) achieving an mRS score of 0 to 1 at 90 days without thrombolysis was 83% based on the Third China National Stroke Registry (CNSR-III) cohort study.[19] A previous pooled analysis[20] of clinical trials showed that the rate of mRS score of 1 or less at 90 days in patients with mild stroke was 90%. Therefore, we assumed that the rate of mRS score of 0 to 1 at 90 days was 85% in the standard care arm, and powered the study to detect a 5% absolute increase to 90% in the prourokinase arm. Based on these assumptions, a total sample size of 1372 patients was calculated with 1-sided $\alpha = .025$ and power of $(1 - \beta) = 0.8$ using PASS, version 16.0, software (NCSS).

Statistical Analysis

The efficacy assessment was carried out in both the intention to-treat population and in the per-protocol population. The intention-to-treat population was defined as all randomly assigned participants. Patients who completed the assigned treatment without major violation of the trial protocol were included in the per-protocol population. The complete data were used to perform the main efficacy analyses without imputation for missing data. The primary efficacy outcome was analyzed using log-binomial regression, with a calculation of relative risk (RR) and a 95% CI. All effects of prourokinase, as compared with standard care, on binary secondary outcomes are reported as RRs with respective 95% CIs that were not adjusted for multiple comparisons and should not be used for hypothesis testing. The shift in mRS score toward a better functional outcome was estimated with the use of an ordinal logistic regression model, and a common odds ratio (OR) with 95% CI was calculated after verification of the proportional odds assumption assessed using the χ^2 test. For the continuous efficacy outcomes, a generalized linear mixed model was fitted and unstandardized beta (B) coefficient with its 95% CI was reported. In sensitivity analysis, multiple imputation by fully conditional specification method was done to impute missing data for the efficacy outcomes. Subgroup analyses for the primary efficacy outcome were also conducted based on age (<75 vs ≥75 years and <80 vs ≥80 years), stroke severity at baseline NIHSS score less than 3 and greater than or equal to 3 to 5 (inclusive), time from onset to treatment 0 to 3.0 hours (inclusive), 3.0 to 4.5 hours (inclusive), diabetes (yes vs no), and hypertension (yes vs no). Post hoc analyses of outcomes were performed with the use of log-binomial regression, with adjustment for baseline NIHSS score and time from onset to treatment. A post hoc subgroup analysis of the primary end point was added; subgroups were defined according to age (<65 vs ≥65 years), quantifying events (stroke vs transient ischemic events vs mimics), and disabling stroke (Reexamining Acute Eligibility for Thrombolysis, or TREAT, Task Force definition,[21] which formed part of the PRISMS trial assessment of nondisabling symptoms in eAppendix 6 in Supplement 3; yes vs no). Safety outcomes were assessed in the safety population with the use of a log-binomial regression model to estimate the RRs with respective 95% CIs. If safety outcomes were extremely infrequent or rare, the Fisher exact test was performed instead. In the safety population, patients who received any amount of prourokinase were assigned to the prourokinase group; all other patients who received standard care

Figure 1. Enrollment and Randomization of the Patients



CT, computed tomography; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

were assigned to the control group. A 2-sided *P* value <.05 was considered to indicate statistical significance. A study-level meta-analysis was performed to pool outcomes of patients with nondisabling stroke in the PUMICE study with those from previous phase 3 trials, using the random-effects DerSimonian-Laird model. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Trial Population

From November 2022 through December 2023, a total of 3836 patients underwent screening at 89 centers in China. Of these patients, 1446 (37.7%) were enrolled in the trial; 723 were randomly assigned to receive prourokinase and 723 to receive standard care. Median (IQR) age was 65.9 (57.7-72.7) years, 498 were female (34.4%), 948 were male (65.5%). The majority of patients (1411 patients) were identified as having Han Chinese ethnicity (97.6%); of the remaining patients, 4 were Hui (0.3%), 12 were Man (0.8%), 5 were Miao (0.3%), 8 were Zhuang (0.6%), and 6 were other ethnicity (0.4%). Standard care included both aspirin and clopidogrel in 650 of 723 patients (90%) (eTable 1 in Supplement 3). One patient was lost to follow-up, and the per-protocol analysis included 1396 patients after exclusion of 23 patients in the prourokinase group and 27 in the standard care group who had serious protocol violations (700 vs 696 in the prourokinase group and standard care group, respectively)

Table 1. Characteristics of the Patients at Baseline

Characteristic	No. (%)	
	Prourokinase (n = 723)	Standard care (n = 723)
Age, median (IQR), y	65.9 (57.6-73.2)	65.9 (58.0-72.2)
Sex		
Female	244 (33.7)	254 (35.1)
Male	479 (66.3)	469 (64.9)
Han Chinese ethnicity[a]	704 (97.4)	707 (97.8)
Medical history		
Hypertension	537 (74.3)	524 (72.5)
Diabetes	171 (23.7)	192 (26.6)
Dyslipidemia	207 (28.6)	215 (29.7)
Previous stroke/TIA	191 (26.4)	200 (27.7)
Atrial fibrillation	40 (5.5)	35 (4.8)
Coronary heart disease	150 (20.7)	157 (21.7)
NIHSS score before randomization, median (IQR)[b]	3.0 (2.0-4.0)	2.0 (1.0-3.0)
0-2	304 (42.0)	367 (50.8)
3-5	419 (58.0)	356 (49.2)
Disabling		
Yes	86 (11.9)	76 (10.5)
No	637 (88.1)	647 (89.5)
Qualifying event		
Ischemic stroke	651 (90.0)	674 (93.2)
TIA	70 (9.7)	46 (6.4)
Mimics	2 (0.3)	3 (0.4)
TOAST classification		
Large artery atherosclerosis	290 (40.3)	281 (38.9)
Cardioembolic	14 (2.0)	22 (3.0)
Small artery occlusion	389 (54.1)	390 (53.9)
Undetermined cause	17 (2.4)	19 (2.6)
Other determined cause	9 (1.3)	11 (1.5)
Time from symptom onset to randomization, median (IQR), min	176.0 (133.0-215.0)	168.0 (123.0-208.0)
Time from symptom onset to CT, median (IQR), min	130.0 (87.0-176.0)	124.0 (78.0-171.0)
Time from symptom onset to treatment, median (IQR), min	187.0 (142.0-225.0)	184.0 (138.0-223.0)
0-3 h	339 (46.9)	354 (49.0)
3-4.5 h	384 (53.1)	369 (51.0)
Door to needle time, median (IQR), min	57.0 (40.0-80.0)	
ASPECTS, median (IQR)	10 (9-10)	10 (9-10)
CT angiography before randomization	10 (1.38%)	10 (1.38%)
Large vessel occlusion[c]	3	3
Intracranial large vessel occlusion[c]	3	2
Endovascular treatment	8 (1.1)	2 (0.3)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT score; CT, computed tomography; mRS, modified Rankin scale; NIHSS, National Institutes Health Stroke Scale; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

[a] Ethnic group was reported by the patient and verified by identification card. Of the remaining ethnicities, 4 were Hui (0.3%), 12 were Man (0.8%), 5 were Miao (0.3%), 8 were Zhuang (0.6%), and 6 were other ethnicity (0.4%).

[b] Scores on the National Institutes of Health Stroke scale (NIHSS) range from 0 to 42, with higher scores indicating a greater neurological deficit.

[c] Within the patients with CT angiography.

(**Figure 1**). The reasons for exclusion from participation, as well as details regarding the protocol violations that occurred during the trial, are provided in Figure 1. There were 20 patients who had CT angiography before randomization, and 5 of them had intracranial large vessel occlusion. Baseline demographic, clinical characteristics, and time measures were similar in the 2 groups except the median (IQR) NIHSS score at randomization (prourokinase, 3.0 [2.0-4.0] vs standard care, 2.0 [1.0-3.0]) (**Table 1**).

Primary Outcome

The proportion of patients with excellent functional outcome (defined as an mRS score ≤1) at 90 days was 88.5% (639 patients) in the prourokinase group and 91.0% (658 patients) in the standard care group (RR, 0.97; 95% CI, 0.94-1.01; *P* = .12) in the intention-to-treat analysis (**Table 2**). Sensitivity analyses using multiple imputation for missing data regarding the primary outcome were also neutral (eTable 3 in Supplement 3). The results of the per-protocol analysis were similar (eTable 4 and eFigure 1 in Supplement 3). No significant differences were identified in subgroup analyses of the primary outcome in the full analysis set (**Figure 2**). The results of post hoc subgroup analyses of the primary outcome according to age, qualifying event, and disabling stroke are provided in eFigure 2 in Supplement 3, showing there was no treatment effect heterogeneity in the absolute risk of mRS score of 0 to 1 at 90 days across these subgroups.

Secondary Outcomes

For secondary outcomes, the results are detailed in Table 2. The distribution of mRS score at 90 days in the prourokinase group did not differ from that of the standard care group (common OR, 1.01; 95% CI, 0.82-1.25) (Table 2 and **Figure 3**). Early neurological recovery at 24 hours was more frequent with prourokinase (RR, 1.26; 95% CI, 1.13-1.40). The trial was not powered for conclusions to be made on the basis of these analyses, and the analyses were not adjusted for multiplicity. The results of post hoc analyses of functional outcomes that were adjusted for baseline NIHSS score time from onset to treatment are provided in eTable 2 in Supplement 3.

Safety Outcomes

Symptomatic intracranial hemorrhage (sICH) within 36 hours after randomization occurred in 5 patients (0.7%) in the prourokinase group and in 0 patients in the standard care group (Fisher exact test *P* = .06) (Table 2). Moderate to severe bleeding occurred in 6 patients (0.8%) in the prourokinase group and 1 patient (0.1%) in the standard care group (RR, 5.95; 95% CI, 0.72-49.39). All-cause mortality within 90 days was 2.3% (17 of 723 patients) in the prourokinase group and 1.4% (10 of 723 patients) in the standard care group (RR, 1.69; 95% CI, 0.78-3.66). The incidence of other adverse events and serious adverse events did not differ substantially between the 2 groups (eTables 5 and in Supplement 3).

Meta-Analysis

In a post hoc analysis, a study-level random-effects meta-analysis of 4 published phase 3 trials, including data from the

Table 2. Efficacy and Safety Outcomes[a]

Outcomes	No.	No. (%)		Effect estimate (95% CI)	*P* value
		Prourokinase	Standard care		
Primary outcome					
No disability (mRS ≤1) at 90 d[b]	1445	639/722 (88.5)	658/723 (91.0)	0.97 (0.94 to 1.01)	.12
Secondary outcomes					
Functional improvement [ordinal distribution of mRS at 90 d], median (IQR)	1445	0 (0-1)	0 (0-1)	1.01 (0.82 to 1.25)	.90
Functional independence (mRS ≤2) at 90 d	1445	673/722 (93.2)	688/723 (95.2)	0.98 (0.95 to 1.01)	.11
Early neurological improvement at 24 h[c]	1441	400/718 (55.7)	320/723 (44.3)	1.26 (1.13 to 1.40)	<.001
Barthel Index 75-100 at 90 d[d]	1418	675/706 (95.6)	684/712 (96.1)	0.995 (0.97 to 1.02)	.67
EQ-5D-5L score at 90 d, median (IQL)[e]	1419	90 (85-100)	90 (85-100)	−0.22 (−2.10 to 1.66)	.82
Lawton IADL score at 90 d, median (IQL)[f]	1418	8 (7-8)	8 (8-8)	−0.05 (−0.21 to 0.11)	.53
Safety outcome					
SICH within 36 h[g]	1446	5/726 (0.7)	0/720 (0)	NE	
All-cause mortality at 90 d	1446	17/726 (2.3)	10/720 (1.4)	1.69 (0.78 to 3.66)	.19
Moderate to severe bleeding at 90 d[h]	1446	6/726 (0.8)	1/720 (0.1)	5.95 (0.72 to 49.4)	.10

Abbreviations: ECASS III, European Cooperative Acute Stroke Study III; EQ-5D-5L, EuroQoL 5-Dimension 5-Level Questionnaire; IADL, Lawton Instrumental Activities of Daily Living; mRS, modified Rankin scale; NE, not estimated; NIHSS, National Institutes Health Stroke scale; SICH, symptomatic intracranial hemorrhage.

[a] B coefficient with its 95% CI was reported using a generalized linear mixed model for the continuous efficacy outcomes.

[b] Scores on the mRS range from 0 to 6, with higher scores indicating greater disability.

[c] Early neurological recovery defined by an improvement in NIHSS score of 4 or more points compared with the initial deficit or a score of 1 or less at 24 hours.

[d] The Barthel Index ranges from 0 (totally dependent) to 100 (patient performs self-care and mobility without assistance), with higher scores indicating greater functional independence.

[e] EQ-5D-5L, designed to measure health-related quality of life.

[f] The IADL scale ranges from 0 to 8, with higher scores denoting higher capability to perform instrumental activities of daily living.

[g] SICH was defined according to the ECASS III trial (any apparently extravascular blood in the brain or within the cranium associated with clinical deterioration, defined by an increase of 4 points or more on the NIHSS from the baseline or within 7 days, or that led to death and was identified as the predominant cause of the neurologic deterioration).

[h] Severe or moderate bleeding was defined according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (Global Utilization) criteria.

PUMICE trial limited to those without clearly disabling deficits/symptoms when TREAT Task Force criteria[21] were retrospectively applied, showed that thrombolytic was inferior to standard care in terms of the primary outcome (RR, 0.97; 95% CI, 0.95-0.99) and increased the risk for sICH (RR, 4.83; 95% CI, 1.63-14.28) and death (RR, 2.78; 95% CI, 1.49-5.20) in nondisabling mild stroke (eFigure 3 in Supplement 3).

Discussion

In this phase 3 randomized clinical trial, patients with mild ischemic stroke treated with intravenous prourokinase within 4.5 hours of the time they were last known well had similar rates of excellent functional outcome and sICH to patients treated with standard care. No differences were observed between the 2 groups regarding other secondary outcomes or across subgroup analyses.

In this trial, the baseline age range, admission NIHSS score, and the time from symptom onset to treatment of the patients with mild stroke were comparable with those of the ARAMIS trial,[8] and the rates of the primary outcome at 90 days were similar in these 2 trials. However, no disability (mRS score 0-1) at 90 days in our trial was more frequent in both the thrombolytic and the standard care groups compared with the PRISMS trial.[7] The efficacy disparity may be explained by the different percentage of Asian patients included (100% vs 0.3%) and differing comorbidity profiles. The increased excellent functional outcomes in the control group may be attributed to the standard care with dual antiplatelet therapy recommended in Chinese and US guidelines for this population when thrombolytics are not used.[22] Compared with the PRISMS,[7] ARAMIS,[8] and our present trial, the TEMPO-2 trial[9] had the lowest rate of excellent functional outcome, not only in the thrombolytic group but also in the medical care group. The TEMPO-2 trial only included patients with intracranial occlusion or a perfusion abnormality, which may explain the worse outcomes. Although recanalization was higher with tenecteplase, this did not translate to improved functional outcomes. An increase in mortality was driven by nonstroke-related factors. The baseline imbalance of NIHSS score between the 2 arms may account for a difference in early neurological improvement given a 4- or more point improvement in NIHSS or NIHSS score of 1 or less. Regarding the safety outcomes, the frequency of sICH in our trial (0.7%) was similar to that in the ARAMIS trial (0.9%)[8] and also comparable with other studies of Chinese patients with mild stroke who were treated with alteplase (0%-1.0%).[23,24] The low rate of sICH may be related to definition and the ethnicity of the population. We have retrospectively applied the TEMPO-2[9] trial definition, which classified sICH in 1.1% (8 of 726 patients) with prourokinase and not substantially different from the 8 of 432 patients (1.9%) observed in the TEMPO-2 trial with tenecteplase.

Figure 2. Relative Risk (RR) of Modified Rankin Scale Score of 0 to 1 at 90 Days (Primary Outcome) in Prespecified Subgroups

Subgroup	No. with event/total (%)		RR (95% CI)
	Prourokinase	Standard care	
Overall	639/722 (88.5)	658/723 (91.0)	0.97 (0.94-1.01)
Age, y			
<80	605/676 (89.5)	619/676 (91.6)	0.98 (0.94-1.01)
≥80	34/46 (73.9)	39/47 (83.0)	0.89 (0.72-1.11)
NIHSS score			
<3	279/303 (92.1)	343/367 (93.5)	0.99 (0.94-1.03)
3-5	360/419 (85.9)	315/356 (88.5)	0.97 (0.92-1.02)
Time from onset to treatment, h			
0-3	310/339 (91.4)	324/354 (91.5)	1.00 (0.95-1.05)
3-4.5	329/383 (85.9)	334/369 (90.5)	0.95 (0.90-1.00)
History of diabetes			
Yes	142/171 (83.0)	172/192 (89.6)	0.93 (0.85-1.01)
No	497/551 (90.2)	486/531 (91.5)	0.99 (0.95-1.02)
History of hypertension			
Yes	468/537 (87.2)	469/524 (89.5)	0.97 (0.93-1.02)
No	171/185 (92.4)	189/199 (85.0)	0.97 (0.92-1.03)

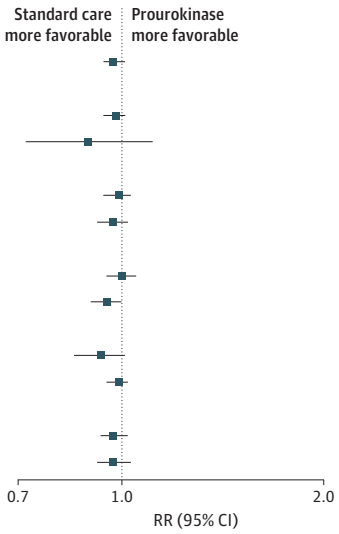
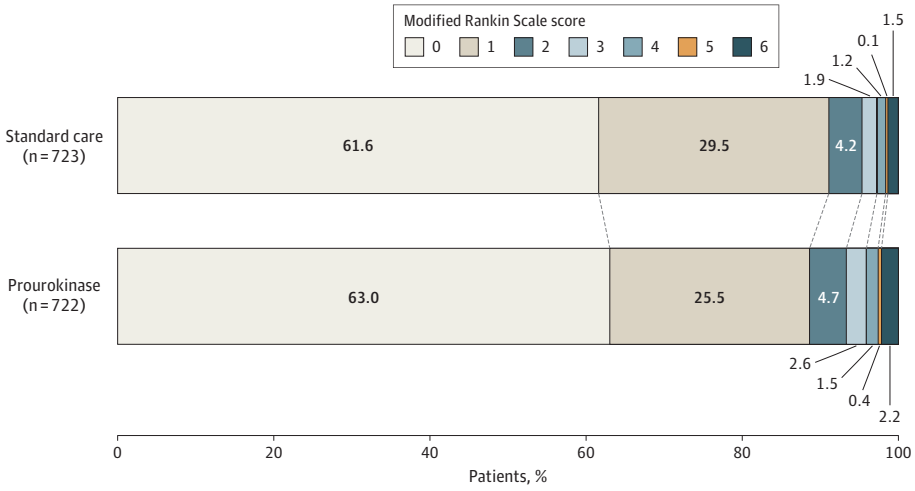


Figure 3. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population)



Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 = symptomatic but not disabled, 2 = disabled but independent, 3 = dependent but ambulatory, 4 = not ambulatory nor capable of body self-care, 5 = requiring constant nursing care, and 6 = death. Percentages may not total 100 because of rounding.

The PRISMS[7] and ARAMIS[8] trials uniquely limited participants to those with nondisabling stroke symptoms among the mild (NIHSS score 0-5) group. PRISMS operationalized the TREAT Task Force guideline[21] based on the clinician and patient deciding together that the symptoms at presentation were not clearly disabling, such that the patient would be likely to perform basic activities of daily living and return to prior employment, if applicable. ARAMIS required less than or equal to 1 point on single-item scores of the NIHSS with the exception of the consciousness item, which was required to be a score of 0 in at the time of randomization. Applying the TREAT Task Force definition, only 11% of our participants were classified as having disabling symptoms, too few to reliably assess outcomes in this subgroup. Approximately 90% of patients in the PUMICE trial had nondisabling symptoms. When the results from the patients in PUMICE who met TREAT Task Force guideline nondisabling criteria were pooled with previously published trials, thrombolysis using alteplase, tenecteplase, or prourokinase was inferior to standard care for the primary outcome (mRS 0-1) (eFigure 3 in Supplement 3) and increased the risk of sICH and death. This provides robust evidence from trials performed in multiple countries that thrombolysis should not be given to patients with nondisabling mild stroke.

Limitations

This study had several limitations. First, we were unable to access a reliable source of prourokinase placebo, hence, the open-label trial design. However, assessors were blinded to treatment allocation. Second, CT angiography was performed in a limited group of patients. For the trial recruitment, we did not require sites to detect large vessel occlusion in patients because

CT angiography is not part of the screening process before thrombolytic therapy according to current guidelines in China. Noncontrast CT scan is mostly used in clinical practice and shortens the door to needle time. However, patients with mild acute ischemic stroke and with large vessel occlusion, although a minority, may be more prone to stroke progression and thus may require further study.[19,20] Although the TEMPO-2 trial investigating thrombolysis in patients with vessel occlusion or focal perfusion lesion demonstrated no benefit, the rates of stroke progression and rescue endovascular thrombectomy were lower than expected.[9] The efficacy and safety of endovascular therapy in these patients will be assessed in the ongoing Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW) and Minor Stroke Therapy Evaluation (MOSTE) trials. Third, the studies included in the meta-analysis used varying definitions of nondisabling and other inclusion/exclusion criteria.

Conclusions

In conclusion, in the PUMICE randomized clinical trial, thrombolysis with prourokinase was not superior to standard care to improve the functional outcomes for patients with mild ischemic stroke within 4.5 hours of symptom onset and had a similar safety profile.

ARTICLE INFORMATION

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