Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

POST-UK (Adjunctive Intra-Arterial Urokinase After Successful Endovascular Thrombectomy in Patients With Large-Vessel Occlusion Stroke): Study Protocol of a Multicenter, Prospective, Randomized, Open-Label, Blinded-End Point Trial

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BACKGROUND: Intra-arterial infusion of an adjunctive thrombolytic agent after macrovascular recanalization by endovascular thrombectomy was regarded as a promising strategy to promote outcomes of patients with stroke. Given the characteristics of urokinase as an affordable, available, and widely applied medication, especially in Eastern countries, this trial aims to assess the safety and efficacy of intra-arterial urokinase as adjunct to endovascular thrombectomy in improving outcomes among patients with anterior large-vessel occlusion stroke after excellent to complete reperfusion.

METHODS: The POST-UK (Adjunctive Intra-Arterial Urokinase After Successful Endovascular Thrombectomy in Patients With Large Vessel Occlusion Stroke) trial is a multicenter, prospective, randomized, open-label, blinded-end point trial conducted in China. The planned sample size is 498. Those eligible patients with anterior circulation large-vessel occlusion stroke and achieving excellent to complete reperfusion by endovascular thrombectomy are planned to be consecutively randomized in a 1:1 ratio to the experimental group (a single dose of intra-arterial urokinase) or to standard of care.

RESULTS: The primary outcome is a freedom from disability (modified Rankin Scale score of 0–1) at 90±7 days. The safety outcomes are mortality within 90±7 days and symptomatic intracranial hemorrhage within 48 hours.

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Clinical Trial Registration Information: www.chictr.org.cn (Unique identifier: ChiCTR2200065617).

Stroke: Vascular and Interventional Neurology is available at: www.ahajournals.org/journal/svin

CONCLUSION: The POST-UK trial will provide valuable insight of efficacy and safety of intra-arterial urokinase in patients with large-vessel occlusion stroke after achieving excellent to complete reperfusion by endovascular thrombectomy.

Key Words: adjunctive therapy ■ endovascular thrombectomy ■ intra-arterial urokinase ■ randomized trial ■ trial protocol

In recent decades, the annual number of disability and deaths attributable to ischemic stroke increased substantially worldwide, especially in low-income and lower-middle-income countries.[1] Endovascular thrombectomy (EVT) has achieved level 1A recommendation for select patients in current stroke guidelines.[2] However, <40% of patients with ischemic stroke caused by large-vessel occlusion (LVO) are disability free at 90 days despite excellent to complete reperfusion (expanded Thrombolysis in Cerebral Infarction [eTICI] scale 2c-3) by EVT.[3] In addition to baseline infarct volume, the outcomes of patients with LVO are determined, in part, by the degree of infarct growth after intervention, caused by insufficient reperfusion for microcirculation and microcirculation.[4] With visible distal emboli, 1% to 10% of the target artery territory remains hypoperfused among patients with an eTICI 2c technical outcome. In those with eTICI 3 technical outcome, normal cerebral angiogram findings are not necessarily indicative of an effective perfusion of the microvascular bed.[5] A post hoc analysis of 3 trials reported that the prevalence of microcirculatory dysfunction after satisfactory reperfusion of EVT was >25%.[6]

As visible thrombi in distal arteries and small unobservable thrombi within the microcirculation impaired perfusion status, intra-arterial infusion of an adjunctive thrombolytic agent after EVT was regarded to be a promising strategy to decrease the incidence of disability after macrovascular recanalization by EVT. Recently, the CHOICE (Chemical Optimization of Cerebral Embolectomy) trial administered intra-arterial alteplase among patients after successful EVT and demonstrated that this therapeutic strategy could significantly improve the rate of excellent outcome.[5] However, the CHOICE trial was prematurely terminated because of the lack of availability of the placebo, which might have introduced potential bias. Compared with alteplase, urokinase (UK) has received recommendation as an efficient and safe intra-arterial adjunctive medication for EVT in clinical guidelines in East Asia.[7] Because of the low price and the availability of customized packaging suitable for arterial thrombolysis, UK has gained widespread use, especially in eastern countries. Data from the INtra-arterial FIbriNolytics In ThrombectomY (INFINITY) registry showed that administration of intra-arterial UK as adjunct to EVT was associated with improving angiographic reperfusion among patients with failed or incomplete reperfusion, and is associated with better outcomes than intra-arterial alteplase among patients with LVO.[8,9] However, there is currently no randomized controlled trial evaluating the effect of intra-arterial UK after successful EVT in patients with LVO.

Therefore, given the characteristics of UK as an affordable, available medication, especially in Eastern countries, we conducted the POST-UK (Adjunctive Intra-Arterial Urokinase After Successful Endovascular Thrombectomy in Patients With Large Vessel Occlusion Stroke) trial, to investigate the efficacy of intra-arterial UK after successful recanalization with respect to functional outcomes as well as its safety, including symptomatic intracranial hemorrhage and mortality. We hypothesized that intra-arterial UK after successful EVT would improve the clinical outcomes of patients with LVO compared with EVT alone.

METHODS

Data in this study are available from the corresponding author by a reasonable request.

Design

The POST-UK trial is a superiority designed. investigator-initiated, multicenter, prospective, randomized, clinical trial with open-label treatment and blinded end point assessment. The trial logo is shown in Figure 1. This trial was registered at www.chictr.org.cn

Figure 1. Trial logo. POST-UK indicates Adjunctive Intra-Arterial Urokinase After Successful Endovascular Thrombectomy in Patients With Large Vessel Occlusion Stroke.

(ChiCTR2200065617). The trial was designed in compliance with the Declaration of Helsinki. This study was approved by the Human Research Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University, and all participating centers. This study included 35 stroke centers across China. The key criterion for a qualifying participating center was the performance of at least 60 mechanical thrombectomy procedures with the use of stent-retriever or contact aspiration devices annually, and all participating neurointerventionalists should have had >3 years' experience and performed at least 50 EVTs. The trial flowchart is shown in Figure 2.

Inclusion Criteria

The POST-UK trial inclusion criteria are as follows:

1. Age ≥18 years;
2. LVO confirmed by computed tomography angiography/ magnetic resonance angiography/ digital subtraction angiography (intracranial segment of the internal carotid artery, middle cerebral artery M1 or M2 segment);
3. Presenting acute ischemic stroke symptoms within 24 hours of onset (last known well);
4. Baseline National Institutes of Health Stroke Scale (NIHSS) score ≤25;
5. Baseline Alberta Stroke Program Early CT (Computed Tomography) Score ≥6 based on noncontrast computed tomography if the time from onset (last known well) was within 6 hours; Alberta Stroke Program Early CT Score ≥7 or met the DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) study criteria (infarct volume of <70 mL, ratio of volume of ≥1.8, and an absolute penumbra volume of ≥15 mL) or met the DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) study criteria (I: aged ≥80 years, NIHSS score ≥10, infarct volume <21 mL; II: aged <80 years, NIHSS score ≥10, infarct volume <31 mL; III: aged <80 years, NIHSS score ≥20, infarct volume of 31 to <51 mL) within 24 hours;
6. Treated with EVT resulting in an eTICI score ≥2c;
7. Written informed consent (by patients or legally authorized representative).

Exclusion Criteria

1. Intracranial hemorrhage confirmed by computed tomography or magnetic resonance imaging on admission;
2. Treated with intravenous thrombolysis or contraindication to intravenous thrombolysis (except time to therapy)[10];
3. Prestroke modified Rankin Scale (mRS) score ≥2;
4. Vessel rupture, dissection, or contrast extravasation during the procedure;
5. Procedure time >90 minutes;
6. More than 3 passes of thrombectomy device;
7. Women who are pregnant or in lactation;

Nonstandard Abbreviations and Acronyms

CHOICE	The Chemical Optimization of Cerebral Embolectomy
eTICI	expanded Thrombolysis in Cerebral Infarction
EVT	endovascular thrombectomy
LVO	large-vessel occlusion
UK	urokinase
POST-UK	Adjunctive Intra-Arterial Urokinase After Successful Endovascular Thrombectomy in Patients With Large Vessel Occlusion Stroke

CLINICAL PERSPECTIVE

What Is New?

- We initiated a large, multicenter, prospective, randomized, open-label, blinded-end point trial to give a high level of evidence of the efficacy of low-dose intra-arterial urokinase among patients with stroke after achieving excellent to complete reperfusion by endovascular treatment.

What Are the Clinical Implications?

- This study represents a study protocol of a prospective, multicenter, open-label, blinded-end point trial that was conducted at nearly 35 sites in China, which investigated the effects of intra-arterial urokinase among patients after successful endovascular therapy. If positive, this study could provide a significant change to the clinical management of patients with acute ischemic stroke who underwent endovascular therapy.

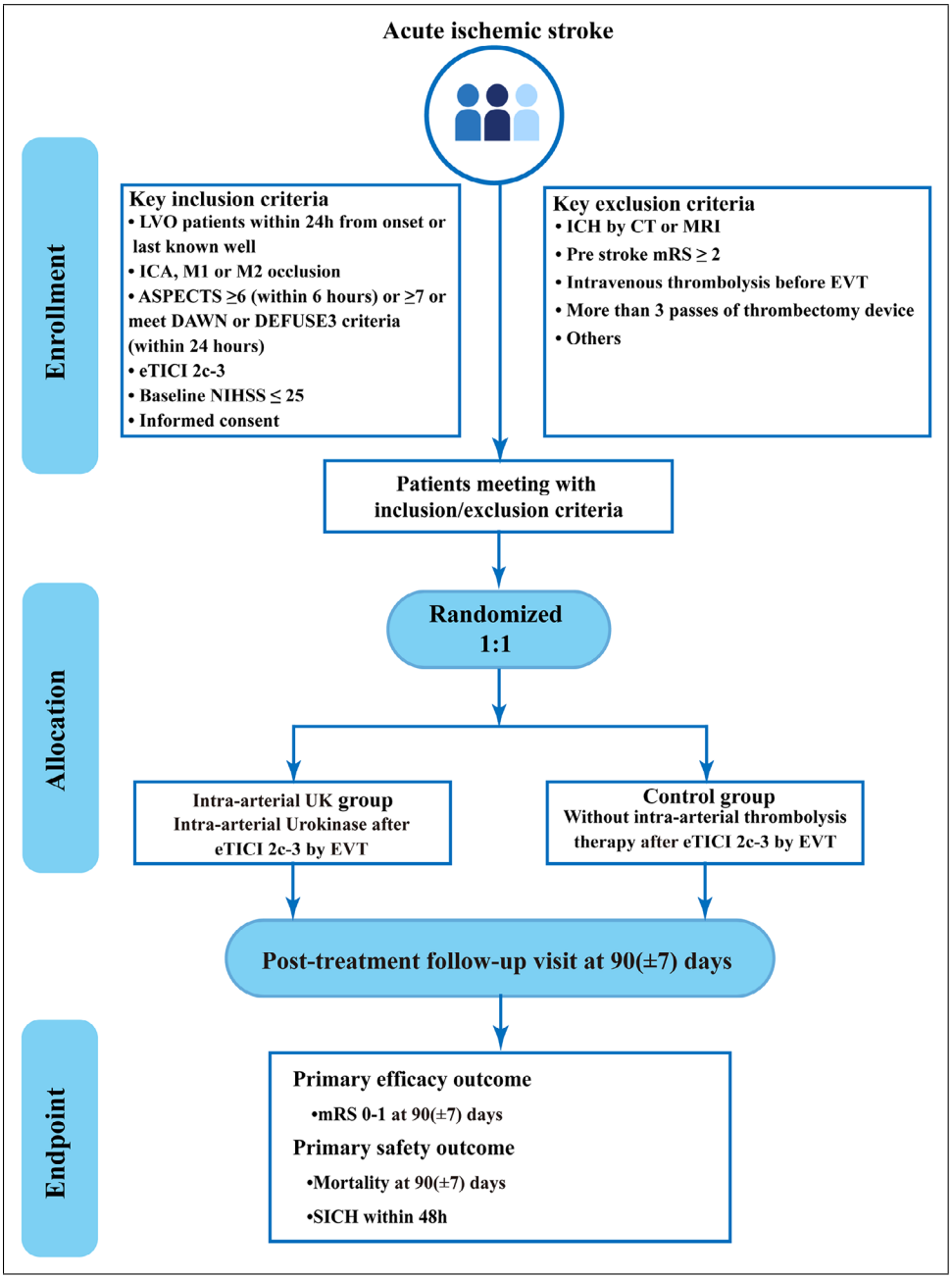

Figure 2. Study flowchart. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Sore; CT, computed tomography; DAWN, DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; eTICI, expanded Thrombolysis in Cerebral Infarction; EVT, endovascular thrombectomy; ICA, intracranial segment of the internal carotid artery; ICH, intracranial hemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging; m1/m2, the m1/m2 segment of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage; and UK, urokinase.

8. Severe contrast allergy or absolute contraindication to iodinated contrast;
9. Systolic blood pressure >185 mm Hg or diastolic pressure >110 mm Hg, and cannot be controlled by antihypertensive drugs;
10. Known genetic or acquired bleeding diathesis, lack of anticoagulant factors, or oral anticoagulants with international normalized ratio >1.7;
11. Blood glucose <2.8 mmol/L (50 mg/dL) or >22.2 mmol/L (400 mg/dL)

12. Platelets $<90\times10^9$/L;
13. Bleeding history (such as gastrointestinal and urinary tract bleeding) in the prior 1 month;
14. Chronic hemodialysis and known severe renal insufficiency (glomerular filtration rate <30 mL/min or serum creatinine >220 μmol/L [2.5 mg/ dL]);
15. Life expectancy <6 months;
16. Patient who cannot complete 90-day follow-up;
17. Intracranial aneurysm or arteriovenous malformation;
18. Brain tumors with mass effect on brain imaging;
19. Participating in other clinical trials.

Randomization

After confirming patient eligibility and obtaining written informed consent, randomization is immediately conducted through a web-based application (www.jinlingshu.com). Eligible patients are randomly assigned to the intra-arterial UK group or the control group in a 1:1 ratio using a permuted block randomization method with randomly selected block sizes of 2, 4, or 6. The randomization procedure is web based and runs on mobile devices or web page platforms.

Treatment

Both treatment arms received EVT. The modality of EVT, including stent retrievers, aspiration, balloon angioplasty, stent deployment, or various combinations of these approaches, is determined as per standard local protocols. After randomization, patients in the UK group receive intra-arterial UK (100 000 IU) through a distal access catheter or microcatheter located proximal to the original occlusion (eg, internal carotid artery, M1, or M2 for 10–15 minutes). Patients randomized to the control group will terminate the procedure without additional intra-arterial thrombolysis therapy.

Efficacy End Points

The primary end point is defined as mRS score 0 to 1 at 90±7 days after randomization.

The secondary end points are:

1. mRS score 0 to 2 at 90±7 days;
2. Level of disability (shift analysis of mRS score) at 90±7 days;
3. The change of the NIHSS score at 5–7 days or discharge if earlier from baseline;
4. European Quality Five-Dimension scale score at 90±7 days.

Safety End Points

A follow-up imaging, including noncontrast cranial computed tomography scan or magnetic resonance imaging scan within 48 hours after randomization, was performed to determine whether intracranial hemorrhage occurs. The safety end points are the following:

1. Mortality at 90±7 days;
2. Symptomatic intracranial hemorrhage within 48 hours according to the modified Heidelberg Bleeding Classification[11,12];
3. Any intracranial hemorrhage within 48 hours

Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board, comprising 3 experts (a neurologist, a neurointerventionist, and a biostatistician independent of the overall study statistician), was established to oversee the overall conduct of this trial. Members of the Data and Safety Monitoring Board will not participate in the trial or be affiliated with the study sponsors. The Data and Safety Monitoring Board will meet annually and monitor trial progress. The experts in Data and Safety Monitoring Board will review the incidence of symptomatic intracranial hemorrhage and serious adverse events to ensure the safety of enrolled patients.

Sample Size Estimate

On the basis of the preceding the Endovascular Treatment With vs Without Tirofiban for Patients with Large Vessel Occlusion Stroke trial, we assumed that the proportion of excellent functional outcome (mRS score 0–1) was 32.8% in the control group.[13] With a 18.6% absolute difference of the mRS 0–1 in the CHOICE trial, we conservatively estimated a 13% difference between the control group and the treatment group, which indicated the proportion of mRS 0–1 in the treatment group would be 45.8%.[13,14] To demonstrate a 13% absolute difference with a type 1 error α of 0.05 (2-tailed) with a power of 83%, a sample size of 472 patients would be needed (236 patients per group). To take into account a 5% attrition rate, a total of 498 patients was required (249 per group). This sample size calculation was performed on PASS (NCSS, LLC, Kaysville, UT) version 15.0.

Statistical Analysis

The primary end point will be analyzed using generalized linear model, which compares the proportion of patients with an excellent outcome (mRS score 0–1) at 90 days between the 2 treatment groups and generates the estimate of risk ratio and its 95% CI as

the measurement of treatment effect. The estimate will be adjusted for age, baseline NIHSS score, baseline Alberta Stroke Program Early CT Score, occlusion sites, and time from onset to randomization. The secondary outcomes and safety outcomes will be analyzed using generalized linear models or assumption-free methods as applicable,[15] with the same adjusting method for the covariates listed above used for the primary outcome analysis. Missing values for baseline characteristics and outcomes will be reported. Adjusted and unadjusted estimates of treatment effects with corresponding 95% CIs will be reported. All analyses will use a 5% 2-sided level of significance. The primary analyses will be based on the intention-to-treat principle. The per-protocol analyses will also be performed as supplemental analysis. Statistical analyses will be performed using SAS 9.4 and R 4.3.0. The trial results will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized trials. All analyses will be detailed in the statistical analysis plan, which will be finalized before the unblinding of the study data.

DISCUSSION AND SUMMARY

With the increase of stroke-related disability and death worldwide, especially in lower-income and lower-middle-income countries, exploring cost-effective strategies to improve outcomes of LVO is needed.[16] Hence, the multicenter, prospective, randomized clinical trial of POST-UK aims to investigate whether the low-dose widely available clinical thrombolysis agent, UK, confers benefit as adjunctive therapy to EVT among patients with LVO who achieved excellent to complete reperfusion by EVT.

Approved by the National Medical Products Administration in China, UK has been recommended in the latest Chinese stroke guidelines for intravenous thrombolysis use in patients with acute ischemic stroke.[17,18] At less than one-tenth the cost of alteplase, UK has gained widespread use, especially in the lower-income and lower-middle-income countries.[19] As only a small dose of thrombolytic agent is required for intra-arterial thrombolysis, the low dose packaging of UK facilitates its application in EVT.[20] Preclinical evidence also showed that UK upregulates blood-brain barrier tight junctions and has a favorable effect on matrix metalloproteinases, potentially lowering the risk of bleeding.[21] Compared with intravenous alteplase, a meta-analysis reported that intravenous UK was as safe and effective in the treatment of acute ischemic stroke.[19] For intra-arterial thrombolysis, a study comprising 311 patients showed a numerically lower rate of symptomatic intracranial hemorrhage and numerically higher rate of favorable outcomes after intra-arterial UK than alteplase after EVT.[8] However, up to now, there has been no clinical trial dedicated to the use of intra-arterial UK in the management of patients after successful reperfusion with LVO.

The application of 100 000 IU of UK in our trial was based on a review of prior literature. Pilot studies reported that 100 000 IU of UK could improve the prognosis among patients with LVO, and it was also effective in preventing new blood clots.[22–24] Moreover, the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan trial showed that intra-arterial dose ranges of UK between 120 000 and 600 000 IU for fibrinolysis of middle cerebral artery occlusion was safe. We selected a lower dose of intra-arterial UK because in contrast to MELT, patients in POST-UK already had successful recanalization.[25] As the mean dose for intra-arterial alteplase in the CHOICE trial was 16.65 mg, our intra-arterial UK dose of 100 000 IU was proportional to the alteplase dose.[14,25]

To minimize the risk of intracranial hemorrhage, we included patients after imaging screening and we excluded patients who had received intravenous thrombolysis.[26,27] We excluded patients with >3 passes of a thrombectomy device as this can be associated with higher risk of endothelial injury with greater instrumentation of the vessel.[28] With that, 3 passes of a thrombectomy device took ≈90 minutes, and procedure time >90 minutes was tightly associated with poor outcomes; we also excluded patients with procedure time >90 minutes to technically guarantee that the enrolled patients could benefit from intral-arterial thrombolysis. On the basis of the subgroup analysis from the CHOICE trial, which did not show an improvement of outcomes among patients with eTICI 2b with intra-arterial thrombolysis, only patients with eTICI of 2c to 3 were enrolled in the current trial because of their lower frequency of symptomatic intracranial hemorrhage compared with patients with eTICI 2b, although the *P* value for interaction was not significant.[14]

We acknowledge limitations in the current trial. First, the treatment assignment is open label, which may lead to potential assessment bias in the study outcomes. To mitigate this limitation, independent and blinded adjudication of the primary outcome assessment at 90 days was used. Independent core laboratory adjudication of imaging results with readers blinded to treatment assignment will also be conducted. Moreover, prespecified secondary analysis on the imaging profile (including infarct volume, delayed reperfusion, and brain edema) will be performed. Second, this study has excluded patients who received intravenous thrombolysis or had intravenous thrombolysis contraindication to reduce the risk of intracranial hemorrhage, which might introduce possible selection bias when enrolling patients. Third,

the sample size of our trial was based on the results of a phase 2b randomized trial of modest sample size, with a risk difference of 18.6%.[14] The present trial was designed with the risk difference of 13% in the primary outcome. Although our treatment effect calculation may have been overestimated, the sample size of this study is by far the largest of similar research to date.[29]

The POST-UK trial will provide pivotal data to assess the efficacy and safety of intra-arterial UK as adjunct to excellent to complete reperfusion by EVT in patients with anterior circulation LVO.

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Received August 5, 2024; Accepted September 18, 2024

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Acknowledgments

None.

Author Contributions

Jeffery Saver reports consulting fees for advising on rigorous and safe clinical trial design and conduct from Biogen, Boehringer Ingelheim, Genentech, Johnson&Johnson, Phenox, Phillips, Rapid Medical, and Roche. There are no competing interests for the other authors.

Sources of Funding

This clinical trial is sponsored by (1) National Natural Science Foundation of China (No. 82271349, 82001264, 82071323), (2) Natural Science Foundation of Chongqing (No. CSTB2024NSCQ-MSX0359), (3) Chongqing Technology Innovation and Application Development Project (No. CSTB2022TIAD-KPX0160), and (4) China Postdoctoral Science Foundation (No. 2023M740444). The study drug was provided by Wuhan Humanwell Pharmaceutical Co Ltd, Wuhan, China. The sponsors had no role in the study design, data collection, analysis, interpretation, drafting or, submission of this article.

Disclosures

Thanh N. Nguyen and Raul G. Nogueira serve on the Editorial Board of S:VIN. Editorial Board Members are not involved in the handling or final disposition of submissions.

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