



Treatment with intravenous alteplase in ischaemic stroke patients with onset time between 4.5 and 24 hours (HOPE): protocol for a randomised, controlled, multicentre study

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ABSTRACT

Background While intravenous thrombolysis is recommended for patients who had an acute ischaemic stroke (AIS) within 4.5 hours of symptom onset, there are few randomised trials investigating the benefits of thrombolysis beyond this therapeutic window.

Aim To determine whether patients who had an AIS selected with the presence of potentially salvageable tissue on CT perfusion at 4.5–24 hours after stroke onset (for stroke with unknown onset time, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) will benefit from intravenous thrombolysis.

Design HOPE is a prospective, multicentre, randomised, open-label blinded endpoint trial with the stage of phase III. The treatment allocation employs 1:1 randomisation. The treatment arm under investigation is alteplase with standard therapy, the control arm is standard therapy. Eligibility imaging criteria include ischaemic core volume ≤ 70 mL, penumbra ≥ 10 mL and mismatch $\geq 20\%$.

Study outcomes The primary outcome is non-disabled functional outcome (assessed as modified Rankin Scale score of 0–1 at 90 days).

Discussion HOPE is the first trial to investigate whether intravenous thrombolysis with alteplase offers benefits in patients who had an AIS presenting within 4.5–24 hours, which has the potential to extend time window and expand eligible population for thrombolysis therapy.

INTRODUCTION AND RATIONALE

Over the last decade, intravenous thrombolytic therapy has been the cornerstone treatment for patients who had an acute ischaemic stroke (AIS), which greatly improved clinical outcome and reduced mortality.^{1–2} In spite of the effectiveness and safety of intravenous thrombolysis (IVT), merely 5%–30% of patients who had an AIS are treated with IVT.^{3–5} The most recent American Heart Association/American Stroke Association (AHA/ASA) AIS guidelines recommend

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While intravenous thrombolysis is recommended for patients who had an acute ischaemic stroke (AIS) presenting within the 4.5-hour time window, the benefit of thrombolysis beyond this therapeutic window is unknown.

WHAT THIS STUDY ADDS

⇒ HOPE trial will address the question whether intravenous thrombolysis offers benefits in patients who had an AIS presenting within 4.5–24 hours after onset if they meet the imaging standard of CT perfusion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ HOPE has the potential to extend time window and expand the eligible population for intravenous thrombolysis.

that patients who had an AIS should receive IVT within 4.5 hours from stroke onset.⁶ This short recommended therapeutic window for thrombolysis is one of the major reasons limiting the utilisation of IVT.

Fortunately, extending time window for reperfusion therapy by identification of salvageable tissue on imaging is feasible theoretically and practically. It has been reported that for patients with good collaterals, the time left for ischaemic tissue to be salvaged could last up to 42 hours.⁷ Other substantial evidences also suggested that potentially salvageable brain tissue might persist over 24 hours.^{8–9} Multiple randomised controlled trials (RCTs) have demonstrated that imaging-based selection of patients with extended time window to receive reperfusion therapy is safe and effective.^{10–13} The EXTEND trial¹¹ and subsequent meta-analysis¹⁴ also provided strong evidence that selected patients with

perfusion mismatch profile presenting within 4.5–9 hours from stroke onset still obtained overall net benefits from IVT. Perfusion mismatch criteria in these analyses included estimated ischaemic core volume <70 mL, ischaemic penumbra volume >10 mL and hypoperfusion/ischaemic core volume >1.2 . Moreover, the therapeutic time window for endovascular recanalisation treatment has been expanded to 24 hours in 2018 AHA/ASA guidelines since the publication of DAWN and DEFUSE3.¹⁵ The secondary analysis of the DAWN study supported the clinical benefit of endovascular therapy in patients who had a stroke with witnessed onset (6–24 hours).¹⁶ Albers further analysed the data of HERMES, DAWN and DEFUSE3 trials, and found non-inferior treatment effects of late-window endovascular therapy compared with early-window therapy.¹⁷ The small core required in late-window trials and slow infarct growth might account for the benefits of reperfusion therapy in late-window studies. In addition, Wheeler *et al* also found that infarct continued to evolve for nearly 40 hours post onset in patients who had a stroke without reperfusion, suggesting possibility of rescuing viable tissue in late window.⁹ Furthermore, several studies have tried to expand the therapeutic window over 24 hours since the time last known to be normal. Thrombectomy was found to be associated with significantly higher odds of functional independence compared with medical management in patients presenting beyond 24 hours.¹⁸ Also, the safety and functional outcomes of reperfusion therapy beyond 24 hours were comparable to reperfusion therapy between 6 and 24 hours.^{19,20} Thus, we can hypothesise that selection of patients using perfusion mismatch imaging profile may permit further extension of the therapeutic window for IVT.

Therefore, we presume that patients who had an AIS presenting with potentially salvageable tissue may benefit from IVT during the time window of 4.5–24 hours. Due to wide application of CT among distinct stroke centres, CT perfusion is chosen for evaluation of core and penumbra to select appropriate candidates for IVT in this study. Overall, this trial aims to investigate whether patients who had an AIS within 4.5–24 hours after symptom onset (for stroke with unknown onset time, the midpoint of the time

last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) can benefit from IVT if they meet the standard of CT perfusion screening (estimated ischaemic core volume ≤ 70 mL, ischaemic penumbra volume ≥ 10 mL and mismatch $\geq 20\%$).

METHODS

Hypothesis

Patients who had an AIS presenting within 4.5–24 hours after onset (for stroke with unknown onset time, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) with evidence of salvageable tissue might benefit from IVT.

Design

HOPE is a multicentre, prospective, randomised, open-label, blinded endpoint, phase III trial. Patients are randomised into treatment or control group with 1:1 proportion. The treatment arm under investigation is alteplase with standard therapy, the control arm is standard therapy. Patient flow is presented in figure 1. The first patient was recruited in June 2021.

Participating centres and patient population

To qualify for participation, centres should meet the following minimum criteria: (1) local tertiary hospitals, (2) capable of performing IVT and completes more than 30 IVTs for patients who had an AIS each year and (3) the interval time from door to needle is less than 60 min.

Patients presenting with clinical signs of AIS within 4.5–24 hours (for stroke with unknown onset, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) are enrolled. Eligibility imaging criteria include ischaemic core volume ≤ 70 mL, penumbra ≥ 10 mL and mismatch $\geq 20\%$ (as evaluated by CT perfusion). For patients with major artery occlusion, the decision for endovascular treatment is made prior to randomisation.

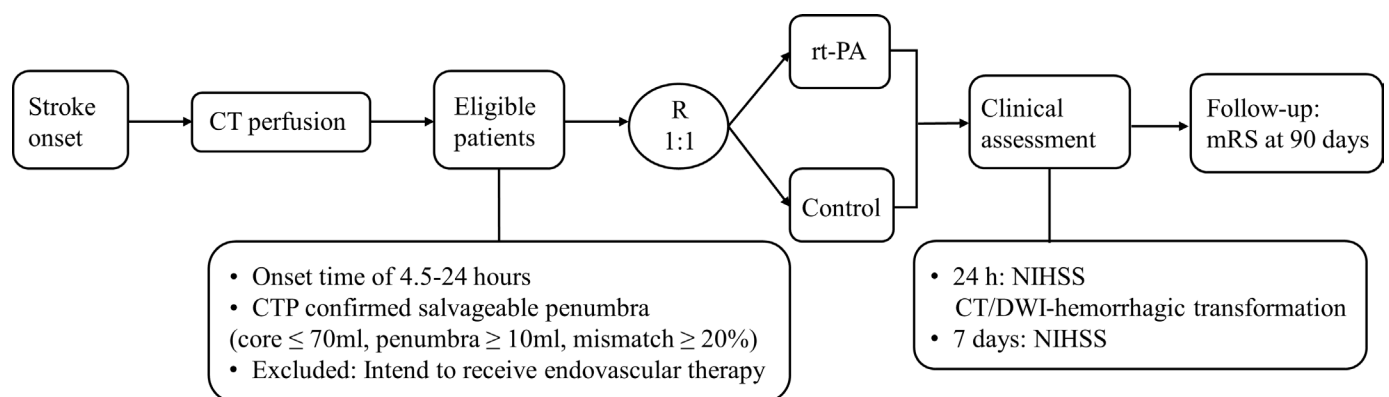


Figure 1 Trial flow chart. CTP, CT perfusion; DWI, diffusion-weighted imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; R, randomisation; rt-PA, recombinant tissue plasminogen activator.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Patients presenting with clinical signs of AIS within 4.5–24 hours from symptom onset (for stroke with unknown time of onset, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of sleep onset or the time last known to be well and wake up time).	1. Intracranial haemorrhage shown on CT.
2. Age over 18 years.	2. Large (more than one-third of the territory of MCA) region of clear hypodensity on CT scan.
3. NIHSS range from 4 to 26.	3. Prestroke mRS score of >1.
4. Imaging inclusion criteria: ischaemic core volume ≤ 70 mL, penumbra ≥ 10 mL and mismatch $\geq 20\%$ (as evaluated by CT perfusion).	4. Other contraindications for alteplase.*
5. Informed consent from patient, family member or legally responsible person depending on local ethics requirements.	5. Intend to undertake endovascular therapy.
	6. A life expectancy of less than 3 months.
	7. Any other condition that could significantly increase the risk of severe bleeding (such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura). The judgement is left to the discretion of investigators.

*Other contraindications for alteplase is in accordance with the latest Chinese guidelines for AIS management (detailed in online supplemental materials).
 AIS, acute ischaemic stroke; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Patients who choose to receive endovascular therapy are excluded. Selection criteria (inclusion/exclusion criteria) are detailed in [table 1](#).

Randomisation

Patients are randomised and allocated to either treatment or control arm using a secure, web-based randomisation system. Randomisation will be stratified by centre. Study outcomes assessors are blinded to treatment assignment.

Intervention

The study intervention is the administration of recombinant tissue plasminogen activator (0.9 mg/kg (maximum 90 mg), 10% of total dose bolus over 1 min, followed by an infusion of the remaining 90% over 60 min). Patients in both groups will be treated at acute stroke units (or intensive care unit based on individual patient circumstances) according to the latest Chinese guidelines for AIS management.²¹

Clinical and imaging evaluation

The schedule of assessments for this trial is described in [table 2](#). Neurological functional deficits will be assessed by an experienced neurologist blinded to the radiographic findings and treatment allocation. At baseline, 1 day and 7 days, the National Institutes of Health Stroke Scale (NIHSS) score will be assessed. At 90 days, the modified Rankin Scale (mRS) assessment will be performed via structured telephone interview.

Patients will have CT perfusion performed at baseline. Hypoperfusion is determined as time to maximum >6 s, and core as relative cerebral blood flow $<30\%$. Penumbral mismatch is the area subtracting core from hypoperfusion area. The volume of core and mismatch will be calculated automatically by the locally used perfusion analysis software, including Siemens workstation, GE workstation, RAPID, MISTar, F-Stroke and so on.

The presence of haemorrhagic transformation, parenchymal haemorrhage (PH) and symptomatic haemorrhagic transformation will be evaluated on diffusion-weighted imaging/CT according to the Heidelberg definition at 24 hours.²²

Primary outcome

The primary outcome is non-disabled functional outcome assessed as mRS score of 0–1 at 90 days.

Secondary outcomes

1. Independent recovery assessed as mRS score of 0–2 at 90 days.
2. Dependent but ambulatory recovery assessed as mRS score of 0–3 at 90 days.
3. Recovery assessed by categorical shift in mRS at 90 days.
4. The change of the NIHSS score from admission to 1 day.

Table 2 Schedule of assessments

	Study period			
	Randomisation	Postrandomisation		Follow-up
Time point	Baseline	24 hours	7 days	90 days
Informed consent form	✓			
Demographic data	✓			
Comorbidity and medical history	✓			
NIHSS	✓	✓	✓	✓
Vital signs	✓			
Routine laboratory assessments*	✓	✓		
Imaging	CTP	NCCT/DWI	NCCT/DWI	
Adverse event assessment		✓	✓	
Modified Rankin Scale	Pre-stroke			✓
Barthel Index				✓
EUROQOL 5D-5L				✓

*Routine laboratory assessments include coagulation profile, complete blood count and clinical chemistry (glucose, lipid profile, electrolytes, urea).
CTP, CT perfusion; EUROQOL 5D-5L, EuroQoL 5-dimensions 5-level; DWI, diffusion-weighted imaging; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale.

5. The change of the NIHSS score from admission to 7 days.

Safety outcome

1. Symptomatic haemorrhagic transformation at 24 hours.
2. PH at 24 hours.
3. All-cause death at 90 days.

Data collection and management

Patient data for each individual are documented in the archived case record form (CRF) and enter into a web-based trial database. The data transfer between browser and database will use a secure and encrypted connection, and access to the database will be password protected. The monitor will check the CRF for completeness and consistency.

Data monitoring body

Trial progress and patient safety will be monitored by an independent data monitoring committee periodically. The committee will determine whether amendment or early termination is needed. If the exclusion criteria need to be modified, for example, the evolved indications for thrombectomy, we will make amendments and submit the revised protocol to the local human ethics committee.

Sample size estimates

The sample size was estimated according to the results of the previous observational cohort at the coordinating centre, which included patients presenting with clinical signs of AIS within 4.5–24 hours of stroke onset (with the same eligibility criteria as HOPE trial). Overall, 62 patients (34 receiving IVT, 28 receiving standard therapy)

were included in the observational cohort. No significant difference was found in age, onset time and baseline NIHSS score between groups, and the proportion of mRS 0–1 at 90 days in the experimental group and the control group was 35% and 21%, respectively. Based on a 15% drop-out rate, 372 patients (186 in treatment and control groups, respectively) would be required to detect a significant treatment effect (two-sided, $p=0.05$) with 80% power.

Statistical analyses

The comparison of primary outcome was performed with intention-to-treat analysis. Using binary logistic regression model, the comparison of proportion of non-disabled functional outcome (assessed as mRS 0–1 at 90 days) will be performed between treatment and control groups after adjustment for age, baseline NIHSS score and time from stroke onset to randomisation. Both of the analyses adjusted for confounders and unadjusted will be carried out. Despite this, adjusted analysis is prespecified as the primary outcome analysis for HOPE trial. An ordinal analysis of the full range (0–6) of the mRS will be undertaken (merging categories 5 and 6) as secondary analysis. Other approaches for secondary outcomes analyses will be employed based on standard statistical principles for qualitative or quantitative variables as appropriate.

The influence on treatment effect by onset time (4.5–9 hours vs 9–24 hours), presence of large or medium vessel occlusion (internal carotid artery, M1 or M2 segment of middle cerebral artery, A1 or A2 segment of anterior cerebral artery, P1 or P2 segment of posterior cerebral artery, basilar artery, vertebral artery), presence of carotid or intracranial stenosis (stenosis $\geq 50\%$),

location of infarct (anterior infarct vs posterior infarct) will be evaluated in subgroup analyses. To explore the efficacy of patients with ‘wake-up’ stroke and those with unknown time of onset, we will conduct subgroup analyses. Considering the differences among various perfusion analysis software in distinct centres, core lab will reconstruct all perfusion images of the patients using a uniform software and perform a sensitivity analysis after excluding patients who do not fulfil the imaging criteria.

DISCUSSION

HOPE will address the question whether patients who had an AIS during the time window of 4.5–24 hours can benefit from IVT on condition that they meet standardised CT perfusion mismatch criteria indicating the presence of salvageable penumbra. Multiple studies have confirmed the benefits of reperfusion therapy in patients who had an AIS with a penumbral imaging pattern, including less infarct growth and more favourable clinical outcomes.^{9 10 17} Furthermore, among patients with early recanalisation, the absence of penumbral pattern was found to be a major factor related to poor outcome.²³ Moreover, the progress of the penumbra into the infarct tissue is highly variable between individuals.⁹ There are many relevant factors including collaterals, metabolic disease and genetic factors.^{24–26} Thus, evaluation of core and penumbra using multimodal imaging offers precise information for individual patients, and selection based on imaging is likely to identify appropriate candidates for IVT.

Hitherto, HOPE trial is the first RCT to investigate the effectiveness and safety of thrombolytic therapy with intravenous alteplase in patients who had an AIS with onset time of 4.5–24 hours, which has the potential to extend time window and expand the eligible population for IVT. In addition, there is scarcely randomised clinical trial investigating reperfusion therapy for Asian population in extended therapeutic window (>4.5 hours). HOPE will add evidence to this end. Furthermore, the imaging techniques used in this trial are those routinely practised in a range of stroke centres, increasing the generalisability of the trial results.

Summary and conclusions

HOPE is a randomised, multicentre, open-label blinded endpoint, phase III trial, which aims to investigate the efficacy and safety of IVT in patients who had an AIS with onset time of 4.5–24 hours. This trial has the potential to extend the time window of IVT and promote thrombolysis utilisation.

Contributors ZL, YZ, YH and ML conceptualised and designed the initial protocol. SY, BCVC and ML amended the initial protocol. ZL and YZ drafted the manuscript. ZC, XZ, YC, L-ST, WZ, HH, KZ and JY contributed to the acquisition of data. All authors have read and approved the final version of the manuscript to be published.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this trial was approved by the Ethics committee 2th affiliated hospital, school of medicine, Zhejiang University (IRB approval number: Yan-2020-657) and all participating centres. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The dataset is available from the corresponding author on reasonable request.

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