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Chemical Optimization of Cerebral Embolectomy 2 (CHOICE 2) trial: study protocol

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ABSTRACT

Rationale The potential value of rescue intra-arterial thrombolysis in patients with large vessel occlusion (LVO) stroke treated with mechanical thrombectomy (MT) remains to be validated in randomised trials.

Aim The Chemical Optimization of Cerebral Embolectomy 2 (CHOICE 2) trial is designed to confirm whether adjunctive intra-arterial alteplase, administered after successful MT, improves clinical outcomes in patients with LVO stroke.

Sample size estimates A total of 440 patients (220 per group) randomised in a 1:1 ratio to receive intra-arterial thrombolysis or not intra-arterial thrombolysis provides 80% statistical power to detect a 14% absolute benefit in the primary endpoint (the proportion of patients achieving modified Rankin Scale (mRS) 0–1 at 90 days), assuming a rate of 40% in the control group, a 5% two-sided type I error. The sample size also provides >95% power for detecting an 18% absolute benefit in secondary imaging endpoints, assuming a 58% rate in the control group.

Methods and design Multicentre, randomised, open, blinded end-point assessment phase III trial. Eligible patients are adults (≥18 years) with symptomatic LVO who undergo MT with successful or complete reperfusion at end of the procedure. Patients in the intervention group will receive a 15 min intra-arterial infusion of alteplase (1.0 mg/mL, maximum dose 20 mg).

Study outcome(s) The primary outcome is the proportion of patients achieving excellent functional outcome (mRS 0–1) at 90 days. Key secondary outcomes are the presence of hypoperfusion on brain CT perfusion at 36±24 hours post randomisation, infarct expansion, Barthel Index and quality of life. Mortality and symptomatic intracerebral haemorrhage will also be evaluated.

Discussion This trial will provide evidence whether rescue intra-arterial thrombolysis improves clinical outcome in patients with LVO stroke who achieve successful or complete angiographic reperfusion following MT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A significant proportion of patients with large vessel occlusion stroke fail to achieve functional independence despite successful mechanical thrombectomy. The Chemical Optimization of Cerebral Embolectomy (CHOICE) trial suggested that adjunct intra-arterial alteplase may enhance brain reperfusion and improve clinical outcomes, but these findings require confirmation in a larger trial.

WHAT THIS STUDY ADDS

⇒ CHOICE 2 is the first phase III trial specifically designed to validate the clinical efficacy of intra-arterial alteplase administered after successful or near-complete recanalisation with mechanical thrombectomy. It uses a rigorous multicentre prospective, randomised, open, blinded end-point assessment design and includes functional and imaging-based endpoints to assess microvascular perfusion and infarct expansion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If positive, CHOICE 2 could establish adjuvant intra-arterial thrombolysis as a standardised reperfusion strategy to improve outcomes in acute stroke, potentially reshaping clinical guidelines and informing future research on microvascular and neuroprotection-targeted therapies.

INTRODUCTION AND RATIONALE

Fewer than half of the patients undergoing mechanical thrombectomy (MT) regain long-term functional independence.[1–8] Alterations in the microvasculature may be major barriers to adequate reperfusion of the ischaemic brain, regardless of successful or complete angiographic reperfusion of the large vessel occlusion (LVO), and constitute the no-reflow

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phenomenon.[9–11] This phenomenon is attributed to microvascular obstruction caused by neutrophils,[12 13] clogging of the perivascular space,[14] distal microembolism[15] or oxidative stress within pericytes[16 17] and arteriolar smooth muscle cells,[18] among other mechanisms. In the Chemical Optimization of Cerebral Embolectomy (CHOICE) trial,[19] the primary outcome (proportion of patients with a modified Rankin Scale (mRS) score of 0–1 at 90 days) was 59.0% in the intra-arterial alteplase arm compared with 40.4% in the placebo arm (adjusted risk difference, 18.4%; 95% CI 0.3% to 36.4%; p=0.047). Furthermore, intra-arterial alteplase enhanced brain reperfusion, limited infarct growth and preserved neuronal integrity.[20] Altogether, the CHOICE investigators concluded that these results were to be interpreted as preliminary and required replication in a larger study.

The CHOICE 2 trial aims to confirm these findings in a larger cohort of patients, evaluating whether intra-arterial alteplase administered after successful or complete recanalisation with MT improves clinical outcomes. The trial also aims to provide evidence to standardise this rescue therapy in clinical practice.

METHODS

Study design

CHOICE 2 is a multicentre, prospective, randomised, open, blinded end-point assessment (PROBE) phase 3 trial in patients who had an acute stroke treated with MT, in which rescue intra-arterial alteplase or not additional intra-arterial therapy are compared (NCT05797792). Allocation at each centre accounts for one stratification factor: prior use of intravenous rt-PA (yes vs no) before MT. Participants are followed for up to 90 days after randomisation.

Patient population

The CHOICE 2 trial is conducted at 14 stroke centres with endovascular capability in Spain.

Inclusion criteria

1. Age ≥18 years.
2. Patients with symptomatic LVO, defined as an acute neurological deficit considered clinically significant by the treating neurologist and associated with intracranial occlusion of the internal carotid artery, anterior cerebral artery or middle cerebral artery, treated with MT resulting in an modified Treatment in Cerebral Ischemia (mTICI) score ≥2b.
3. Randomisation must occur within 24 hours of symptom onset.
4. Premorbid mRS score 0–1, or mRS >1 only when due to non-neurological causes (ie, amputation, blindness).
5. Alberta Stroke Program Early CT Score (ASPECTS) ≥6 on non-contrast CT (NCCT); in patients with symptom onset ≥4.5 hours or unknown onset, advanced imaging (CT perfusion (CTP) or diffusion-weighted MRI) is recommended when available and considered appropriate by the treating neurologist, but not mandatory.
6. Informed consent.

Exclusion criteria (abridged)

1. Baseline National Institutes of Health Stroke Scale (NIHSS) score >25.
2. Any contraindication to rt-PA according to local national guidelines (except the treatment time window).
3. Expected requirement for dual antiplatelet therapy during the first 24 hours after MT.
4. Female who is pregnant or lactating.
5. Presence of any haemorrhage on baseline NCCT/MRI.
6. Brain imaging

Patients undergo an NCCT to exclude intracranial haemorrhage and classification according to the ASPECTS scale <6. Brain CTP or DWI-MRI is recommended (although not mandatory) if symptoms are >4.5 hours. Immediately after completing the study medication, angiographic results are documented using the mTICI score. At 36±24 hours, a follow-up NCCT is performed to detect haemorrhagic complications, and a brain CTP, to assess the prevalence of hypoperfusion and the final infarct volume. A predefined subgroup also undergoes a brain Diffusion-weighted imaging (DWI)/Perfusion-weighted imaging (PWI) MRI at 36±24 hours to correlate MRI and CT maps in detecting hypoperfusion and evaluating final infarct volume.

Randomisation

Randomisation codes assign patients 1:1 between both arms, stratified by site and prior intravenous rt-PA use (no or yes), using a real-time, centralised randomisation system implemented via the CHOICE 2 web platform. Randomisation is conducted through Viedoc's dynamic allocation system based on the Pocock and Simon minimisation algorithm. This method does not rely on fixed block sizes; instead, it continuously analyses treatment assignment distributions within each stratum and applies a weighted probability to minimise imbalance. This approach ensures balanced allocation across groups while maintaining allocation concealment and avoiding predictability.

In CHOICE 2, written informed consent is obtained prior to the endovascular procedure, after neuroimaging confirms the presence of an acute LVO amenable to MT. Randomisation is performed intraprocedurally through a centralised web-based system, and only after successful or near-complete reperfusion is confirmed (defined as an expanded Treatment In Cerebral Infarction (eTICI) score of 2b50, 2b67, 2c or 3). Patients are randomised only if all inclusion criteria are met and no exclusion criteria are present.

For those allocated to the intervention arm, intra-arterial alteplase is administered immediately following randomisation via the existing endovascular catheter. The drug is infused over 15 min, targeting the arterial segment proximal to the previously occluded site, in accordance with the protocol-defined dosing scheme. Final angiographic assessment and definitive eTICI

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scoring are performed after the treatment administration in both study arms, following a standardised imaging protocol that enables blinded adjudication by a central core imaging laboratory.

Intervention

MT is performed according to the standard practice of each centre, including the endovascular techniques currently used, the chosen type of anaesthesia and Conformité Européenne (CE) marked devices. A maximum of three passes/aspirations per vessel, with a total limit of five passes/aspirations per patient, is allowed. Patients fulfilling the study criteria receive or do not receive a 15 min intra-arterial infusion of alteplase (Actilyse®), at a drug concentration of 1.0 mg/mL, with a maximum adjusted dose of 20 mg. The infusion is administered via a distal access catheter in the distal cervical internal carotid artery or just below the intracranial carotid artery bifurcation. Angiographic runs (anteroposterior and lateral views) are recorded at the conclusion of the standard procedure or, for the treatment arm, after the experimental therapy.

Primary outcome

The primary outcome is the proportion of patients who achieve excellent functional outcome, defined as a mRS score of 0–1 at 90 days. This outcome is assessed by video call by central blinded evaluators following a structured questionnaire.

Secondary outcomes

1. Proportion of patients with abnormal hypoperfusion on brain CTP at 36h±24 hours post MT, assessed by blinded evaluators at the Central Imaging Core Lab.
2. Volume of hypoperfusion on brain CTP at 36h±24 hours post MT.
3. Infarct expansion ratio: Ratio of final infarct to initial ischaemic tissue volumes on brain Non-Contrast Computed Tomography (NCCT) at 36±24 hours post MT.
4. Proportion of patients achieving Barthel Scale score of 95–100 at day 90.
5. Quality of life assessed with the EuroQol Group 5-Dimension Self-Report Questionnaire at 90 days.
6. The shift analysis of the mRS, at day 90.

Safety outcomes

1. Mortality at 90 days.
2. Rate of symptomatic intracerebral haemorrhage (sICH), at 36h±24 hours, defined according to European Cooperative Acute Stroke Study (ECASS)-3 criteria as a neurological deterioration of ≥4 points on the NIHSS in association with evidence of intracranial haemorrhage on neuroimaging.

Data monitoring body

All data are entered into an electronic case record form (eCRF) and monitored by external qualified staff. The investigator is responsible for ensuring the prompt and accurate reporting of study data into the eCRF. The eCRF is managed according to general and specific standards of Good Clinical Practice (GCP). Adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities. Once the database is confirmed as complete and accurate, it is locked, and any further modifications require appropriate justification and full traceability. The final data management process includes plausibility checks, consistency reviews and range validations. Any missing data are flagged, and data clarification forms are issued.

The trial is overseen by a steering committee with support from a Contract Research Organization (CRO; currently Avania, formerly Anagram-ESIC). Proper conduct of the study is promoted through regular communication, site visits to investigators and centralised coordination. The patient or their legal representative signs the approved version of the informed consent form at the initiation of MT. Reasons for non-inclusion in CHOICE are documented in monthly screening logs at each participating site.

An independent Data Safety Monitoring Board conducts partially blinded safety monitoring, reviews the incidence of serious AEs (SAEs) and provides safety recommendations to steering committee chair in accordance with predefined stopping rules. The CRO is responsible for monitoring predefined AEs and SAEs.

The Statistical Analysis Plan (SAP) is finalised prior to the first unblinded data review. An Imaging Central Core-lab evaluates all imaging data to independently confirm inclusion and exclusion criteria and to perform an unbiased review of follow-up scans. Cerebral angiograms are centrally assessed using the eTICI score. As part of the safety assessment, all intracranial haemorrhages (whether symptomatic or asymptomatic) are prospectively recorded and centrally adjudicated by the Imaging Core Laboratory in accordance with the ECASS-3 classification system.

A clinical events committee reviews and validates all SAEs during the trial and determines their relationship to the experimental treatment. Finally, a trial coordinating site, composed of three experienced stroke neurologists, provides telephone support to local investigators throughout the study.

Sample size calculation

Based on CHOICE data, enrolling 220 patients per treatment group gives 80% statistical power to detect a 14% absolute benefit in the primary outcome (proportion of patients with mRS score of 0–1 at 90 days), assuming a rate of approximately 40% in the control group and 5% two-sided type I error. The calculations account for a conservative value of 5% study losses, despite all treated randomised patients being included in the main analysis. This margin is intended to ensure adequate power for secondary analyses involving other trial populations. This sample size will also provide at least 95% statistical power to detect an 18% absolute benefit in a key secondary outcome (the proportion of patients with hypoperfusion

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at 36±24 hours on brain CTP) assuming a 58% rate in the control group, using a 5% two-sided type I error.

Statistical methods

The main analysis includes all patients treated as allocated. A detailed SAP will be available before the unblinding of the data (see online supplemental appendix).

The main efficacy endpoint, the proportion of patients with a mRS score of 0–1 at 90 days, will be estimated using a binomial regression model adjusted for the stratification variable (previous intravenous rt-PA use), with the identity link function. Risk difference for 90-day mortality will be analysed using the same method as the primary outcome, and exact 95% CIs will be computed for sICH at 36±24 hours. In addition to the predefined safety endpoints (mortality and sICH), all SAEs, regardless of their causal relationship with treatment, will be prospectively collected, centrally adjudicated and summarised descriptively. Safety conclusions will be based on the full spectrum of serious and non-SAEs. Subgroup analyses use the same binomial model as the primary outcome, excluding the stratification covariate, and interaction terms will be included in additional models to test subgroup-by-treatment interaction. Post hoc sensitivity analyses for the primary endpoint will include adjustment by study site and models exploring random imbalances in baseline covariates. For the primary and binary secondary endpoints, missing data will be treated as treatment failures, irrespective of the reason. The significance level will be set at 0.05 (two-sided). The following prespecified subgroups will be explored in sensitivity analyses:

1. Use of intravenous rt-PA at admission (yes vs no).
2. eTICI 2b50/67 versus TICI 2c/3 at randomisation.
3. MT initiated within 7.3 hours of symptoms onset versus MT performed between 7.4 hours and 24 hours.
4. Baseline serum glucose ≤100 mg/dL versus >100 mg/dL (5.5 mmol/L).
5. Males versus females
6. Patients <90 kg versus patients >90 kg
7. Age ≤80 years vs >80 years.

Ethics and dissemination

The trial is conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines on GCP, and all applicable national regulatory requirements.

DISCUSSION

Despite successful reperfusion achieved by MT, up to half of patients with LVO stroke fail to attain favourable clinical outcome.[1–8] This mismatch between angiographic and clinical success has highlighted the concept of futile recanalisation and has led to growing interest in adjunctive reperfusion therapies to improve outcomes.[10 11] One of the key mechanisms contributing to poor clinical recovery after MT is the no-reflow phenomenon, a term that refers to persistent microvascular hypoperfusion despite macrovascular recanalisation. This phenomenon, described over five decades ago, is now supported by extensive experimental and clinical data.[9] It may be caused by neutrophil infiltration, microvascular thrombosis, pericyte constriction or inflammatory remodelling, all of which impair capillary-level perfusion.[10–18]

The CHOICE trial was the first study to formally explore the concept of adjunctive reperfusion therapy aimed at enhancing microcirculation following successful MT.[19] By administering intra-arterial alteplase after achieving macrovascular reperfusion, CHOICE introduced a novel therapeutic strategy designed to target microvascular dysfunction directly. It provided preliminary evidence that this approach could improve brain reperfusion and lead to better clinical outcomes.[21] This concept originated in the CHOICE trial and has since gained increasing attention as a promising strategy to optimise post-thrombectomy care.[22–24]

The CHOICE 2 trial builds on this foundation, using a rigorous PROBE design and a larger sample size to confirm whether this strategy truly benefits patients. Importantly, CHOICE 2 incorporates both clinical (mRS 0–1 at 90 days) and imaging-based endpoints (CTP-assessed hypoperfusion, infarct expansion), offering a unique opportunity to correlate tissue-level reperfusion with functional outcomes. Furthermore, the inclusion of subgroups based on perfusion patterns, Intravenous thrombolysis (IVT) use, eTICI grade and glucose level, among others, may help identify patient profiles more likely to benefit from adjunct thrombolysis.[25]

CONCLUSIONS

The CHOICE 2 study is designed to generate rigorous evidence to guide best practice in patients with LVOs treated with MT who achieve successful or complete angiographic reperfusion of the previously occluded target artery.

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Contributors ÁC conceptualised, designed and took responsibility for the trial and acted as guarantor. AR and ÁC wrote the first draft of the manuscript. ÁC, AR, XU, SA and FT provided intellectual contribution. AR, XU and SA coordinate the investigators and participating centres as part of the trial coordinating site. ÁC, AR, JB, MW and LSR designed the intra-arterial administration protocol. ÁC, AR, LO and CL designed the neuroimaging protocol. ÁC, FT and ECL designed the clinical events protocol. ÁC, FT, FH-F and JV designed the statistical analysis pipeline. JFAL, AS, MdMF, NPdlO, MC and AD provided intellectual contributions. RD-M, PdlR, PV, RD-M, LD, MDF-C, MH-I, NLH, AM, LM, PC-R, AS, MT, PV and JS contributed as principal investigators by supporting the overall study design and ensuring the local implementation of the clinical trial. All authors reviewed and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval The Clinical Research Ethics Committee of the Hospital Clínic of Barcelona acts as the main Ethics Committee (CEIm) for this research project (HCB/2023/0874). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. No aplica.

Author note The details of the Committees are as follows: Steering Committee: ÁC (Chair), JFAL, MC, MdMF, NPdlO, LSR, FT (Biostatistician). Neuroimaging Core Lab: LO, (Chair), CL, JB, MW. Trial Coordinating Site: AR (Chair), SA, XU. Clinical Events Committee: ECL. Data Safety Monitoring Board (DSMB): AD (Chair), FHF, JV (Biostatistician). Clinical Study Management: ANAGRAM-ESIC. Statistics: Jorge del Campo. Sponsor: Fundació Clínic per la Recerca Biomèdica.

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