CLINICAL STUDY PROTOCOL
CHOICE

CHemical **O**pt**I**mization of **C**erebral **E**mbolectomy in patients with acute stroke treated with mechanical thrombectomy (CHOICE TRIAL)

Study Code: CHOICE
Protocol Version 3.1: December 04, 2020
EudraCT Number: 2018-002195-40
SPONSOR: Fundació Clínic per la Recerca Biomèdica

SUMMARY OF THE TRIAL

Title	**CH**emical **O**pt**I**mization of **C**erebral **E**mbolectomy in patients with acute stroke treated with mechanical thrombectomy (CHOICE TRIAL)
Study Design	Multicenter, randomized, placebo-controlled, double blind, phase 2b trial of acute stroke patients treated with MT, in which two therapies are compared: rt-PA or placebo. Allocation at each center will account for 1 stratum: use of alteplase (yes vs. no) before MT. Subjects will be followed up to 90 days post-randomization
Clinical Site Locations	Catalonia Autonomous Community, Spain
Study Centers	Hospital Clínic de Barcelona (HC) Hospital Universitari de Bellvitge (HB) Hospital Vall d'Hebron (HVH) Hospital de la Santa Creu i Sant Pau (HSP) Hospital del Mar (HM) Hospital Germans Trias i Pujol (HGTP) Hospital Josep Trueta (HJT)
Study Objective	The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion and successful brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b/3)
Subject Population	Patients with symptomatic large vessel occlusion (LVO) in the anterior circulation treated with MT resulting in a mTICI score 2b/3 on cerebral angiography
Enrolment	Patients will be enrolled in the angiosuit by interventionalists or neurologists once a mTICI 2b/3 is confirmed on cerebral angiography. A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least 80% statistical power for the primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm (odds ratio (OR) of 2.33) for a 5% two-sided type I error. This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56%. No study losses are accounted for since all randomised patients will be included in the analysis.

Follow-up	Each patient included will be followed up to 90 days from the stroke
Inclusion Criteria	1. Patients with symptomatic large vessel occlusion (LVO) in the anterior, middle or posterior cerebral arteries treated with MT resulting in a mTICI score 2b/3 at end of the procedure. Patients with an mTICI score 2b/3 on the diagnostic cerebral angiography before the onset of MT are also eligible for the study. 2. Estimated delay to onset of rescue intraarterial rt-PA or placebo administration <24 hours from symptom onset, defined as the point in time the patient was last seen well 3. No significant pre-stroke functional disability (modified Rankin scale 0-1), or mRS >1 that according to the investigator is not related to neurological disease (i.e. amputation, blindness) 4. Age ≥18 5. ASPECTS ≥6 on non-contrast CT (NCCT) scan or MRI if symptoms lasting <4.5 hours or ASPECTS ≥ 6 on CT-Perfusion (CTP) or DWI-MRI if symptoms ≥4.5 <24 hours. 6. Informed consent obtained from patient or acceptable patient surrogate
Exclusion Criteria	1. NIHSS score on admission ≥25 2. Contraindication to IV t-PA as per local national guidelines (except time to therapy) 3. Use of carotid artery stents during the endovascular procedure requiring dual antiplatelet therapy during the first 24h 4. Female who is pregnant or lactating or has a positive pregnancy test at time of admission 5. Current participation in another investigation drug or device treatment study (except observational study i.e.: RACECAT or clinical trials not testing new medical devices or new drugs i.e.IMAGECAT) 6. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency 7. Known coagulopathy, INR >1.7 or use of novel anticoagulants <48h from symptom onset

	8. Platelets <50,000 9. Renal Failure as defined by a serum creatinine >3.0 mg/dl (or 265.2 µmol/l) or glomerular Filtration Rate [GFR] <30 10. Subject who requires hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason 11. Any hemorrhage on CT/MRI 12. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal 13. Suspicion of aortic dissection 14. Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol 15. History of life threatening allergy (more than rash) to contrast medium 16. SBP >185 mmHg or DBP >110 mmHg refractory to treatment 17. Serious, advanced, terminal illness with anticipated life expectancy <6 months 18. Pre-existing neurological or psychiatric disease that would confound evaluation 19. Presumed vasculitis or septic embolization 20. Unlikely to be available for 90-day follow-up (e.g. no fixed home address, visitor from overseas)
Primary Outcome	Proportion of patients with a mRS 0 to 1 at 90 days.
Analysis	The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP / ICH / 363/96)
Safety endpoints	1. Mortality at 90 days 2. sICH rates at 24 hours
Study Timeline	Recruitment period estimated in 24 months F-up per patient: 3 months
Primary Analysis	The primary outcome will be estimated using a log-binomial regression model including the stratification variables, except centre. In the unexpected event that the model does not fit, the Poisson regression model with long-link and robust variance estimator will be used instead.

Steering Committee	Ángel Chamorro (Chair) Sergio Amaro Pere Cardona Antonio Dávalos Juan Macho Joan Martí-Fábregas Laura Oleaga Jaume Roquer Ferrán Torres (Biostatistician) Xabier Urra Joaquín Serena
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Sponsor	Fundació Clínic per la Recerca Biomèdica

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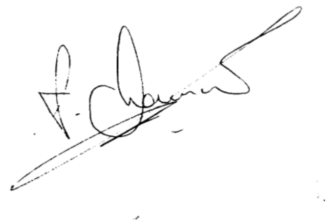
STUDY CODE: CHOICE

Study titled: A phase 2b trial comparing the administration of alteplase or placebo for Reperfusion Injury Control in acute stroke patients secondary to large vessel occlusion treated with mechanical thrombectomy

The signatures on this page indicate review and approval of the final version of the protocol.

By signing this document we confirm that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.



__________________________ December 4,2020

Dr. Ángel Chamorro Date of signature

Chairman/ Sponsor's Representative Name

PROTOCOL SIGNATURE PAGE PRINCIPAL INVESTIGATOR

STUDY CODE: CHOICE

Study titled: CHemical Optimization of Intraarterial Cerebral Embolectomy in acute stroke patients treated with mechanical thrombectomy
The signatures on this page indicate review and approval of the final version of the protocol.

By signing this document we confirm that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

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Principal Investigator's Name

___________________ ___________________

Signature Date of signature

1. ADMINISTRATIVE INFORMATION

Title: **CH**emical **O**pt**I**mization of **C**erebral **E**mbolectomy in patients with acute stroke treated with mechanical thrombectomy (CHOICE TRIAL)

Protocol version: Version 3.1, December 04, 2020

Funding: Marató de TV3

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Funder and Sponsor of the CHOICE trial will have no influence on the study design, collection, management, analysis and interpretation of data, writing of the report and decision to submit the report for publication. Chairs and members of the Executive Committee will perform all these activities.

2. INTRODUCTION

Stroke represents the second single most frequent cause of death for people older than 60 years, the most frequent cause of permanent disability, and the second most common cause of dementia, and uses approximately 3–7% of the total health-care expenditure in high-income countries. By 2050, more than 1.5 billion people in the world will be aged 65 years or older and the global burden of stroke will keep increasing in parallel with the ageing population.[1] Although a remarkable progress has been made in the management of patients with acute ischemic stroke during the past 10 years, with the widespread implementation of specialist stroke units, evidence of the efficacy of intravenous (IV) thrombolytic treatment, and reporting of randomized controlled trials (RCTs) establishing the value of endovascular thrombectomy,[2] stroke still represents the first cause of permanent disability in adult people. In consequence, there is a pressing need to continue investigating new treatments for this devastating disease.

2.1 Background and rationale

2.1.1 Overview of reperfusion therapy in acute ischemic stroke

Intravascular thrombosis remains a leading cause of death and disability for which thrombolysis is the only pharmacological remedy. The thrombolytic, rt-PA, has become essentially synonymous with thrombolysis but its use, or that of one of its longer half-life derivates, has been declining due to its inadequate efficacy in AMI, incompatibility with PCI, limited efficacy and risk of ICH in ischemic stroke, and too high a bleeding risk for most patients with venous thromboembolism. Instead, intra-arterial devices have become the treatment of choice in AMI are becoming more frequently used in ischemic stroke as well. The resort to these time-consuming methods to treat very time-sensitive conditions is a reflection on the inadequacy of current thrombolysis.

The main aim of acute ischemic stroke treatment is to salvage the penumbra or volume of hypo-perfused, non-functional, yet still viable tissue surrounding the infarcted core, and several reperfusion therapies have shown positive clinical results. A meta-analysis of individual patient data from nine randomized trials comparing intravenous alteplase with placebo or open control showed that alteplase increased the odds of a good stroke outcome (i.e., a modified Rankin scale score of zero or one at 3–6 months), with earlier treatment associated with bigger proportional benefit.[3] Accordingly, rapid administration of IV recombinant tissue-type plasminogen activator (rt-PA) to appropriate patients remains the mainstay of early treatment of acute ischemic stroke.[4] However, IV rt-PA induces recanalization in only 40% of the cases,[5] and this rate is even lower in occlusions of the M1 segment of the middle cerebral artery or the intracranial internal carotid artery, where the rate of recanalization is approximately 20% and 10%,[6],[7] respectively.

IA thrombolysis involves administration of high concentrations of thrombolytic agents near the thrombus, utilizing lower doses than systemic administration, which may result in lower systemic complications, and less local neurotoxic effects of thrombolytic agents. The disadvantages of the IA modality include the potential delay required to obtain initial cerebral angiography and position of the micro-catheter for administration of the thrombolytic agent. IA thrombolysis also allows the simultaneous use of mechanical devices to facilitate thrombolysis,[8] and combining the IA delivery with mechanical thrombectomy (MT) increases the surface area exposed to the thrombolytic agents. The concern of delaying treatment onset using the IA route alone led to the initiative of delivering the IA thrombolysis following IV thrombolysis. Thus, the Emergency Management of Stroke (EMS) bridging trial, which had a randomized, double-blind, placebo control design, demonstrated higher recanalization rates (53%) in the combined IV/IA alteplase treatment group than in the IA alteplase group (28%).[9] In this study, 35 patients were treated within 3 hours of symptom onset and received IV rt-PA (0.6 mg/kg, 60 mg maximum, 10% of the dose as a bolus over 1 minute and the remainder over 30 minutes) or placebo. This was followed by immediate cerebral angiography and local IA administration of rt-PA through the catheter if a clot in the appropriate arterial distribution was identified. A maximum local IA dose of 20 mg was given and the infusion was continued for a maximum of 2 hours. In EMS, there was no difference in clinical outcomes between the 2 groups and no significant difference in the rate of symptomatic ICH. Indeed, there were no parenchymal hematomas in the trial; symptomatic ICH within 24 hours occurred in 1 placebo/IA patient only; beyond 24 hours, symptomatic ICH occurred in 2 IV/IA patients only.

The Interventional Management of Stroke Trial III (IMS III) was a PROBE, 2-arm, superiority trial that enrolled 656 patients with a major ischemic stroke who received IV rt-PA within 3 hours of stroke onset.[10] Patients were randomly allocated 1:2 to standard dose IV rt-PA (0.9 mg/kg) or to IV rt-PA 0.6 mg/kg followed by endovascular therapy with a device and/or IA rt-PA, if occlusion persisted and if the endovascular intervention could be begun within 5 hours and completed within 7 hours of onset. For subjects who the study neurointerventionalist elected to treat with the standard micro-catheter infusion of rt-PA, as in the IMS I Pilot Trial, the rt-PA concentration for IA administration was 0.5 mg/1 ml solution (50 mg/100 cc - reconstituted with 50 cc of sterile water without preservatives and diluted to 100 cc total with 50 cc normal saline). A maximum IA dose of 22 mg was administered over two hours of infusion. The trial was stopped early for futility after 656 of projected 900 subjects were enrolled. There was no significant difference in outcome between the IV rt-PA only group and the endovascular group for the primary end point of the percentage of patients with a good outcome as measured by modified Rankin Scale (mRS) score of 0 to 2 or for death at 90 days. Findings in the endovascular-therapy and intravenous rt-PA groups were similar for mortality at 90 days (19.1% and 21.6%, respectively; $P = 0.52$) and the proportion of patients with symptomatic intracerebral hemorrhage within 30 hours after initiation of t-PA (6.2% and 5.9%, respectively; $P = 0.83$).Yet, the IMS III trial showed that the proportion of patients who obtained a mRS score of 2 or less at 90 days of the therapy (primary outcome of the study) increased in parallel with the magnitude of reperfusion measured using the Thrombolysis In Cerebral Infarction (TICI) grade.[11] Thus, the primary outcome occurred in 12.7% of the 55 patients with a TICI score of 0, in 27.6% of the 29 patients with a TICI score of 1, in 34.3% of the 108 patients with a TICI score of 2a, in 47.9% of the 119 patients with a TICI score of 2b, and in 71.4% of the 7 patients with a TICI score of 3 ($P<0.001$). These results highlight the importance of obtaining complete brain reperfusion to maximize the benefits of mechanical thrombectomy.

Prior small case series have demonstrated that IA therapy with thrombolytic agents,[12,13] Mechanical Clot Disruption (MCD),[14] or a combination of IA thrombolytic agents with MCD [15,16] are safe and effective with and without prior full-dose IVT in restoring flow in acute large artery occlusions. Nine IA thrombolytic agents, when used in low doses, have been found to be safe in conjunction with MCD. A series of 8 patients suggested that an IA rt-PA dose up to 40 mg is safe,[17] but these patients did not receive prior IVT. The overall efficacy and safety of IA versus IV thrombolysis in patients with acute ischemic stroke was updated in a recent meta-analysis [18] that showed that IA thrombolysis in patients was significantly more likely to result in a favourable outcome than was IVT. However, other meta-analyses using different study selection criteria found no significant benefit of IA over IV.[19] Altogether, IA thrombolysis initiated within 6 h of stroke onset might be considered in carefully selected patients who have contraindications to the use of IV alteplase, although alteplase does not have US Food and Drug Administration approval for intra-arterial use, and the adverse effects associated with this administration route have yet to be established.[20] Unfortunately, there are no published reports of observational or randomized studies of IA thrombolysis performed *after* MT to attempt improving the perfusion rate of territories distal to the proximal arterial occlusion.

In 2015, several RCTs showed that MT results in complete vessel recanalization in three of four treated patients, and this treatment was superior to IV alteplase in improving stroke outcomes in selected patients with large proximal artery occlusions. [21,22,23,24,25] A comprehensive systematic review and meta-analysis of eight RCTs (totalling 2049 patients) confirmed that MT was associated with an increased likelihood of good outcome (i.e., a modified Rankin scale score of zero to two at 90 days) compared with standard alteplase treatment.[26] Patients receiving alteplase before MT also had a significant improvement in outcome compared with patients who received only one of these treatment approaches (Yarbrough et al. 2015). MT in combination with IA pharmacologic thrombolysis has been associated with higher rates of recanalization.[27] In a recent individual patient data meta-analysis by the HERMES group of patients with large-vessel ischemic stroke, earlier treatment with MT + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months and the clinical benefit became non-significant after 7.3 hours. [28] More recently, the DAWN (Diffusion weighted imaging (DWI) or computerized tomography perfusion (CTP) assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neuro-intervention with Trevo) data was reported.[29] Patients with wake-up and late-presenting stroke were screened and if they met the inclusion criteria (age ≥18 years, NIHSS ≥10, pre-mRS 0–1, time-last-seen-well to randomization 6–24 hours, excluding large infarcts and confirmation of large vessel occlusion on CTA or MRA) underwent imaging with the RAPID software, CTP or DWI. Qualifying patients had to meet the following clinical imaging mismatch criteria: patients' ≥80 years old had to have NIHSS ≥10 with a core <21cc; <80 year old patients had to have NIHSS ≥10 with a core of <31cc or NIHSS ≥20 with a core of <51cc. The symptomatic intracerebral hemorrhage (sICH) rate was 4.8% in the treatment arm versus 3.2% in the control arm. A statistically significant difference was observed in neurological deterioration (defined as greater than 4 points worse on the NIHSS by five days) between the two groups with 10.5% in the treatment arm versus 22.1% in the control arm ($p<0.01$). In the weighted mRS based co-primary outcome, the mean mRS value in the treatment group was 5.5 versus 3.4 in the control group; a 2.1 difference in the weighted mRS score, which is highly significant with a Bayesian probability of superiority of >0.9999 (which is similar to p<0.0001). The co-primary endpoint of 90-day functional independence was 48.6% in the treatment group versus 13.1% in the control group; a 35.5% actual difference, which is highly significant with a Bayesian probability of superiority of >0.9999. This translates to a number needed to treat of 2.8 to achieve functional independence.

Despite the unquestionable value of current reperfusion therapies less than half of the patients that receive MT show permanent benefits. [15–19] A likely relevant reason to these insufficient clinical benefits is the lack of adequate brain reperfusion despite successful recanalization (futile recanalization). In the recent endovascular trials, "successful" brain reperfusion occurred in 75% of treated patients, including a group of 37% of patients who obtained complete reperfusion (mTICI 3 score) and a group of 38% of patients who obtained only near complete reperfusion (mTICI 2b score) on cerebral angiography. Although several studies have shown a graded association between the amount of brain tissue re-perfused and the degree of clinical benefit,[30] the most recent endovascular trials did not report individual stroke outcomes amongst patients with mTICI 2b or 3 scores.

2.1.2 Maximizing brain reperfusion: a target for treatment improvement

Structural and functional alterations in the microvasculature may be major barriers for adequate reperfusion of the ischemic brain regardless of complete recanalization and constitute the no-reflow phenomenon.[31,32] In experimental models, downstream microvascular thrombosis (DMT) may occur early during brain ischemia and before recanalization, and this mechanism may be a major contributing factor to incomplete reperfusion.[33] It is possible that a similar mechanism may limit the therapeutic potential of MT in patients with acute stroke. Originally attributed to spasm or cellular swelling around the vessel wall, the no reflow phenomenon is currently ascribed to microvascular clogging triggered by neutrophils trapped within the microcirculation,[34] clogging of the perivascular space,[35] distal micro-embolism,[36] and oxidative stress generated in pericytes,[37,38] or arteriolar smooth muscle cells.[39] In experimental studies, this clogging was prevented or reversed using genetic or pharmacological manipulations of cell mediated inflammation,[40] but these measures were futile or harmful at the bedside.[41] Considering the nature of these mechanisms, we believe that IA thrombolytic therapy is a pharmacological approach that deserves adequate testing is patients with incomplete reperfusion following MT. Mechanical embolus retrieval does recanalize the occluded larger arteries without considering the status of the distal smaller arteries. However, recanalization of the primary arterial occlusive lesion does not necessarily translate into reperfusion of ischemic tissue through the distal capillaries. IA pharmacologic therapy remains the only possible alternative in such situations to ensure complete angiographic reperfusion to the ischemic tissue.

2.1.3 Justification of CHOICE

While previous studies of improving brain reperfusion using IA thrombolytic therapy were done before the recanalization of a proximal LVO, in this project we intend to administer IA thrombolysis after the successful recanalization of a LVO. Indeed, this temporal approach might prove to be crucial to facilitate a greater access of the drug to the distal vascular bed and thus allow a more effective lytic effect on microcirculatory thrombi.

The current guideline for healthcare professionals from the American Heart Association/American Stroke Association (AHA/ASA) states that the use of salvage technical adjuncts including IA fibrinolysis may be reasonable to achieve a satisfactory angiographic result in patients treated with MT (Class IIb recommendation).[20] Yet, the usefulness, and effectiveness of salvage IA thrombolysis are not well established. The AHA/ASA also recommends that the angiographic technical goal of MT is to achieve a mTICI 2b or 3 scores.[20] Yet, growing evidence shows that combining these two mTICI scores into a single category of angiographic results may be misleading because they may show significant differences in clinical and radiologic outcomes. [11,42,43] To better address this issue, we reviewed recently our own experience, and compared the clinical and radiologic outcomes of patients with a mTICI 3 or a mTICI 2b score at the end of MT.[44] All these patients received stent-retrievers and pre-treatment IV alteplase was administered to approximately one third of the patients. The outcomes were evaluated in multivariate models following the HERMES Collaborators criteria, [28] and the covariates assessed in the models included age, sex, baseline stroke severity, target occlusion location, ASPECTS, pre-treatment IV alteplase, time to recanalization and the collateral score. Between March 2010 and May 2016, 125 of 347 (36%) patients treated with MT at Hospital Clínic of Barcelona met the entry criteria of the study. Contrarily, 222 patients were excluded for (1) a posterior circulation stroke (n = 31); (2) lost to follow-up due to transfer to a referral Primary Stroke Center after MT (n = 113); (3) unavailability of multimodal brain imaging (n = 37); or (4) mTICI 2a/1/0 score at the end of MT (n = 41). Recanalization of the local occlusion occurred within a median (IQR) of 285 (210–369) minutes of symptom onset; 51 (41%) patients achieved an mTICI 2b score and 74 (59%) patients a mTICI 3 score. Patients with final mTICI 2b or 3 scores did not show significant differences in demographics, risk factors, target occlusion location, use of bridging intravenous alteplase before MT, or size of infarct core calculated either with the ASPECTS on NCCT or on CTP (Table 1). Expectedly, a mTICI 3 score was associated with shorter time to recanalization from stroke onset, and less number of device passes. A final mTICI score 3 was more frequent in patients with good leptomeningeal collateral scores, and this association was highly significant in a multivariate model adjusted for the predefined covariates of the study, (odds ratio 2.765 95% CI 1.248–6.123). The primary outcome measure of the study showed that more patients with mTICI 3 were in a better score category on the mRS at 90 days than were patients with mTICI 2b, and this difference was statistically significant in ordinal regression analysis adjusted for confounders (odds ratio 2.018, 95% CI 1.033–3.945).

Excellent outcome at 90 days was reported in 18 (35%) of 51 patients achieving an mTICI 2b score and in 41 (55%) of 74 patients achieving an mTICI 3 score, (adjusted odds ratio 2.739, 95% CI 1.124–6.182). Early dramatic recovery at 24 hours was diagnosed in 25 (49%) patients with mTICI 2b and in 54 (73%) patients with mTICI 3, (adjusted odds ratio 3.078, 95% CI 1.384–6.849). Finally, the mortality and the rate of symptomatic intracerebral hemorrhage did not differ between patients with mTICI 3 or 2b scores. Collectively, this study demonstrated the relevance of achieving an mTICI 3 score at the end of MT to maximize the functional benefits of brain reperfusion. Compared with patients with an mTICI 2b score, patients who achieved a mTICI 3 had better overall health transitions in the full range of the mRS, increased proportions of excellent outcome and early dramatic recovery, less infarct growth and smaller final infarcts. Altogether, these results justify the search of more effective reperfusion therapies and call for a change of current practice recommendations in patients treated with MT indicating that only an mTICI 3 angiographic score should be considered success after MT.

However, whether the superiority of mTICI-3 over mTICI-2b is retained in any patient subgroups has not been fully investigated. A recent study found that mTICI-3 was associated with favorable outcomes when the puncture-to-reperfusion time was <80 minutes (adjusted OR, 2.28; 95% CI, 1.52–3.41), but not when the puncture-to-reperfusion time was >=80 minutes.[45] Whether this occurs because the ischemic core grows into the penumbral region as time passes or because there is no reflow following full reperfusion is not settled. Peri-interventional thrombus fragmentation may occur during mechanical thrombectomy and potentially be accountable for incomplete (<mTICI3) reperfusion.[46] Yet, endovascular treatment of more distally located persisting occlusion despite a mTICI-2b may be associated with a greater risk of periprocedural complications. Further, recent studies showed that even in up to 42.5% patients with final mTICI 3 after MT, it can be found areas of hypoperfusion in 42.5% in CTP perfusion studies performed at the end of the procedure.[47] Although regional opacification of angiography source images implies normal cerebral blood flow visualization of perfusion at the microcirculatory level is limited, yet this may be clinically important. Using Digital Substraction Angiography Perfusion (DSAP), persisting hypoperfusion, reflected in prolonged MTT and Tmax times, may occur despite successful recanalization, graded as TICI 2b or better. This is consistent with the no-reflow phenomenon. It may reflect distal micro-occlusions that are not easily visualized on DSA source images, or dysfunction of the microvascular circulation because of edema and/or pericyte damage impairing perfusion. Overall, at the end of MT, neither angiographic nor clinical evaluation are accurate enough to discriminate those patients who will experience a favourable outcome from those who will not and may need additional therapies. The variable clinical response to full reperfusion TICI grades may be related to the subjectivity of DSA grading. Further, there are subsets of patients with eTICI 2c or 3
reperfusion with outcomes of severe disability or death. Such examples suggest that angiographic outcomes alone have limited utility for clinical outcome prediction.[48]

2.2 OBJECTIVES

The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion but partial brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b/3).

2.3 TRIAL DESIGN

Multicenter, randomized, placebo-controlled, double blind, phase 2b trial of acute stroke patients treated with MT, in which two therapies are compared: rt-PA or placebo. Allocation at each center will account for 1 stratum: use of alteplase (yes vs. no) before MT. Subjects will be followed up to 90 days post-randomization.

3. METHODS

3.1 STUDY SETTING

The CHOICE trial will be performed in Catalonia Autonomous Community, and it will include seven Endovascular Stroke Centers located in Barcelona, Badalona and Girona:

1. Hospital Clínic de Barcelona (HC)
2. Hospital Universitari de Bellvitge (HB)
3. Hospital Vall d'Hebron (HVH)
4. Hospital de la Santa Creu i Sant Pau (HSP)
5. Hospital del Mar (HM)
6. Hospital Germans Trias i Pujol (HGTP)
7. Hospital Josep Trueta (HJT)

3.2 ELIGIBILITY CRITERIA

3.2.1 Inclusion Criteria

1. Patients with symptomatic large vessel occlusion (LVO) in the anterior, middle or posterior cerebral artery treated with MT resulting in an mTICI score 2b/3 at end of the procedure. Patients with an mTICI score 2b/3 on the diagnostic cerebral angiography before the onset of MT are also eligible for the study.
2. Estimated delay to onset of rescue intraarterial rt-PA administration <24 hours from symptom onset, defined as the point in time the patient was last seen well
3. No significant pre-stroke functional disability (modified Rankin scale 0-1), or mRS >1 that according to the investigator is not related to neurological disease (i.e. amputation, blindness)
4. Age ≥18
5. ASPECTS ≥6 on non-contrast CT (NCCT) scan or MRI if symptoms lasting <4.5 hours or ASPECTS ≥6 on CT-Perfusion (CTP) or DWI-MRI if symptoms ≥4.5 <24 hours.
6. Informed consent obtained from patient or acceptable patient surrogate

3.2.2 Exclusion Criteria

1. NIHSS score on admission ≥25
2. Contraindication to IV t-PA as per local national guidelines (except time to therapy)
3. Use of carotid artery stents during the endovascular procedure requiring dual antiplatelet therapy during the first 24h
4. Female who is pregnant or lactating or has a positive pregnancy test at time of admission
5. Current participation in another investigation drug or device treatment study (except observational study i.e.: RACECAT or clinical trials not testing new medical devices or new drugs i.e. IMAGECAT)
6. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency
7. Known coagulopathy, INR > 1.7 or use of novel anticoagulants < 48h from symptom onset
8. Platelets < 50,000
9. Renal Failure as defined by a serum creatinine > 3.0 mg/dl (or 265.2 µmol/l) or glomerular Filtration Rate [GFR] < 30
10. Subject who requires hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason
11. Any hemorrhage on CT/MRI

12. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal
13. Suspicion of aortic dissection
14. Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol
15. History of life-threatening allergy (more than rash) to contrast medium
16. SBP >185 mmHg or DBP >110 mmHg refractory to treatment
17. Serious, advanced, terminal illness with anticipated life expectancy < 6 months
18. Pre-existing neurological or psychiatric disease that would confound evaluation
19. Presumed vasculitis or septic embolization
20. Unlikely to be available for 90-day follow-up (e.g. no fixed home address, visitor from overseas)

3.2.3 Brain Imaging

Patients will have a non-contrast CT scan (NCCT) or brain MRI at hospital admission to rule out the presence of blood and estimate the Alberta stroke program early CT score (ASPECTS) that will be used to select into the trial only patients with ASPECTS $\geq$ 6. Concomitantly, a whole brain CT-Perfusion (CTP) or DWI-MRI will be performed before transfer of the patient to the angio suite. The protocol for CTP acquisition will be harmonized by the Neuroimaging Core Lab as described in the Appendix. Patients will then receive MT according to the general methods described below. At 10 minutes of completion of the experimental therapy the angiographic results will be recorded on anterior-posterior and lateral projections for central scoring according to the modified Treatment of Cerebral Ischemia (mTICI) grading score (See below section 3.3 for further clarification). At 24 $\pm$12 hours of randomization, a NCCT (or MRI) will be performed to assess the presence of early bleeding complications following ECASS3 criteria (Appendix). At 48$\pm$24 hours of randomization, a brain MRI with DWI and T2* sequences will be performed to measure the volume of the infarction, estimate the growth of the infarction and assess the presence of late bleeding complications (Appendix). If a brain MRI cannot be performed for contraindications, intolerance or unavailability, a NCCT will be indicated. The admission NCCT (or MRI), admission CTP (or DWI-MRI), post-MT angiography, 24h NCCT and 48h brain MRI or NCCT will be transferred to the Central Imaging Core Lab (CICL) for storage and reading within 72 hours of image acquisition (Appendix).
Other study visits and study assessments are specified in Appendix 6.5.

3.3 Interventions

Patients with confirmed large vessel occlusion (LVO) of the anterior, middle or posterior cerebral artery and treated with MT will receive alteplase (Actylise®) or placebo if the mTICI score on cerebral angiography is 2b/3. Patients displaying an mTICI score 2b/3 on cerebral angiography before a first pass with an endovascular device could still be eligible for randomization into the study because we define the onset of mechanical thrombectomy as the time of groin puncture.

Endovascular treatment will be carried out according to the usual practice of each center. Once the intracranial occlusion is confirmed, thrombectomy will be performed using any of the techniques currently used, provided that the devices used are CE marked. The use of balloon catheter will be at the discretion of the interventionalist, as well as the thrombectomy system, which may be by aspiration, by means of stent-retriever devices or combination of both techniques. On the contrary, patients treated with devices under study will not be included in CHOICE.

Likewise, the type of anesthesia will be decided by the team that performs the procedure, and none of the options, local anesthesia, sedation or general anesthesia, are grounds for exclusion.

Once the thrombectomy procedure is finished, the cases that meet the inclusion criteria from the point of view of final reperfusion, that is, those with a mTICI 2b/3 will be randomized. The maximum will be six passes or six aspirations for the patient to meet the criteria for inclusion in CHOICE. The thrombectomy procedure will be considered complete once the neurointerventionalist considers that the angiographic result is good enough and it does not seem reasonable by endovascular thrombectomy techniques to continue the procedure to obtain a better revascularization.

Aside from procedurally administered heparinized saline, IV heparin is prohibited until after the 24hour neuroimaging has been performed to minimize the risk of intracranial hemorrhage. Blood pressure should be tightly controlled during the first 24 hours to less than 185/110 mmHg. If TICI ≥2b is achieved, BP goal should be less than 160/90 mmHg. Given the association between hyperglycemia and SICH in patients undergoing IA thrombolysis, a target blood glucose level of less than 160 mg/dL is recommended.

The neurointerventionalist will receive the medication to be injected according to protocol, proceeding to inject said medication through a distal access catheter or microcatheter located proximal to the residual thrombus (if still present) and distally to the origin of the lenticulostriates branches. The administration of placebo / rTPa will be infused for 15 '. The super-selective catheterization of the occluded branch (s) to perform the administration of the medication vs. the injection of said medication from more proximal positions will be at the decision of the neurointerventionalist depending on the difficulty of access, risk of distal catheterization, patient agitation, occluded branches, etc. It should be recorded in the angiography images, that will be sent to the Core Lab, if the placebo / rTPa infusion has been performed from M1 or from any of the bifurcation branches (an image of the position of the catheter from which the placebo / rTPa injection was made has to be sent). It is recommended not to inject the medication / placebo immediately proximal to an occluded artery, without exit, because of the risk of directly accumulating a greater concentration of the drug there.

All the patients will be given a 15 minutes IA infusion at a drug concentration of 1.0 mg/ml. At 15 minutes of IA treatment onset, the infusion will be stopped and the angiographic score assessed. If the angiographic score is improved compared with the baseline score the procedure is terminated, otherwise a new angiographic series will be repeated in 5-10 minutes before the end of the procedure in front and profile projections.

If contrast extravasation occurs during the IA administration of alteplase or placebo, it could be indicative of active bleeding. In that case, IA drug infusion should be stopped immediately.

Furthermore, it is recommended the occlusion of the culprit vessel if contrast extravasation occurs at an accessible vessel

Study drug will be prepared according to the following steps:

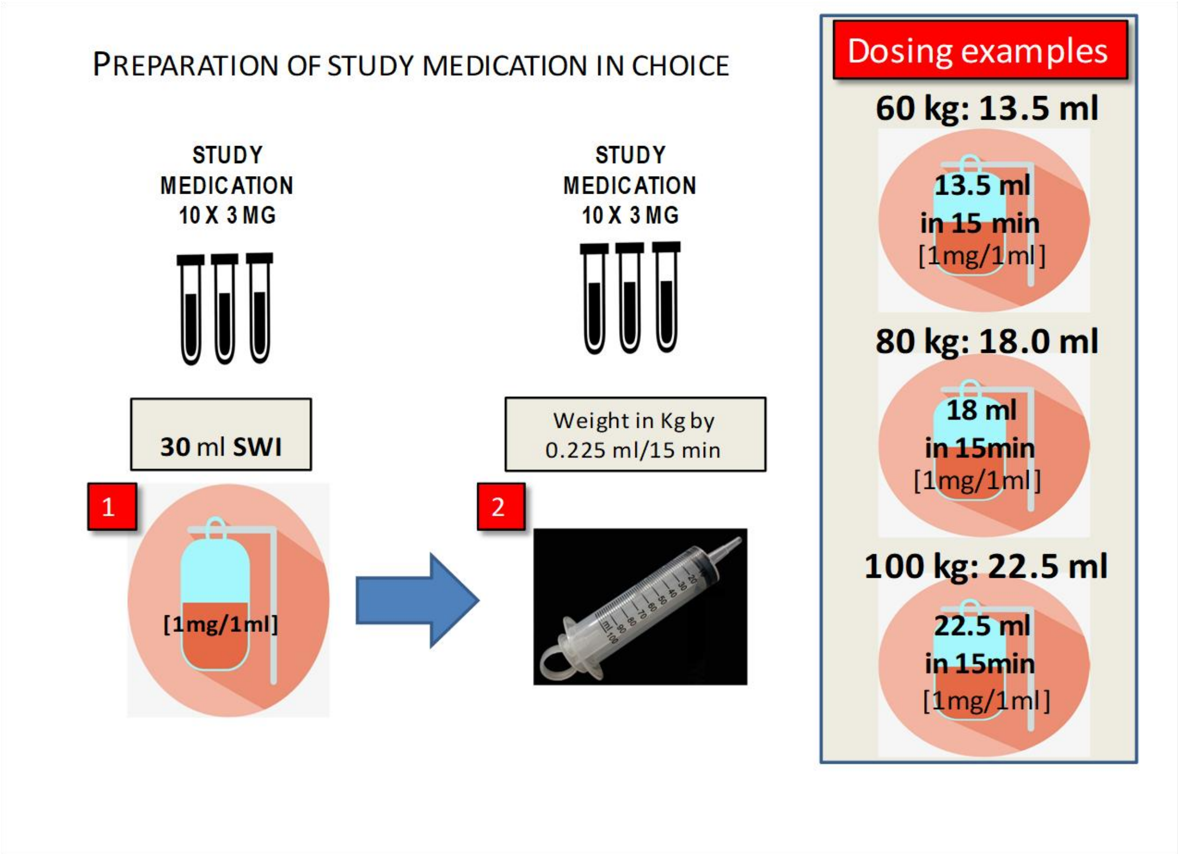
1. Dilute 3 vials of 10 mgs (alteplase or placebo) in 30 cc of sterile water for injection (SWI), to attain a 30 cc solution at a concentration of 1mg/ml
3. Calculate the volume of cc of infusion and therefore the total dose as per the formula:
   (Patient's weight in Kgs multiplied by 0.225)

As shown in the figure, a patient of 80 Kgs will receive 18 cc of infusion for 15 min, totalling a dose of 18 mg of alteplase. A patient of 100 Kgs will receive 22.5 cc of infusion for 15 min, totalling a dose of 22.5 mg of alteplase.

Situations that will lead to NO INCLUSION IN CHOICE: Recovery of the patient ad integrum at the table.

The placebo will consist of a lyophilized white powder containing 0.2 mol/L arginine phosphate, 0.01% polysorbate 80, and pH 7.4 after reconstitution.

Figure



3.3.1 Blinding

The solutions of alteplase or placebo are limpid, transparent and colourless. Alteplase (Actilyse 10 mg powder and solvent for solution for injection and infusion) and placebo will be provided in kind by Boëhringer Ingelheim. The secondary conditioning of the investigation treatment will be performed by Alcura Health Spain S.A.

3.3.2 Concomitant care and interventions prohibited during the trial

Patients will receive alteplase upon hospital arrival if indicated according to each institutional protocol, and always in agreement with European Stroke Organization and national guidelines. The use of anticoagulants and dual antiplatelet therapy will not be permitted during the 24 hours after the administration of the experimental therapy.

3.4 Assignment of intervention. Allocations and sequence generation

Randomization codes will be produced by means of the PROC PLAN of the SAS system, with a 1:1 ratio of assignment between both arms, stratifying by centre, and use of IV alteplase (no or yes) in blocks multiple of 2 elements. The time of randomization will be initiated whenever a full angiogram establishes the patient has an mTICI 2b/3 score. A “Real-Time” randomization procedure will be implemented via the CHOICE Trial Website where the clinical center staffs enter the basic baseline and eligibility information of a subject prior to enrolment. If the subject’s eligibility status is confirmed, the computer program on the server will make the treatment assignment based on the randomization algorithm specified.

3.5 Outcomes

3.5.1 Primary outcome

The primary outcome will be the proportion of patients with a mRS 0 to 1 at 90 days

3.5.2 Secondary Outcomes

4 Proportion of patients with angiographic changes on the eTICI score. To that aim, all the baseline angiographies will be scored at the core lab by central and blinded reviewers using the eTICI and classified as eTICI2b50, eTICI2b67, eTICI2c, and eTICI3. The post treatment angiographies will be scored using the eTICI and classified as “improved”, “worsened” or “unchanged” with regard to the baseline eTICI score.

- The shift analysis of the modified Rankin Scale (mRS), at day 90. The mRS at 90 days will be analyzed using a proportional odds model (POM) that combine into single worst rank the last two categories (5: severe incapacity and 6: death).
- Infarct Expansion Ratio on DWI-MRI (continuous variable), at 48h (+/- 24h) of stroke (Infarct Expansion Ratio (IER): Final infarct to initial ischemic tissue volumes).
- Proportion of patients with/without infarct expansion (dichotomous variable) (Expanding infarct: IER>1.
- Infarction Volume on DWI-MRI, at 48h (+/- 24h) of stroke onset

3.5.3 Tertiary outcomes

- Barthel Scale score of 95 to 100, at day 90
- Ischemic worsening (≥ 4 points in the NIHSS score) within 72 hours of stroke onset not attributable to stroke recurrence
- Quality of life measured with the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-3L) at 90 days

3.5.4 Pre-specified subgroup analysis

Proportion of patients with angiographic changes on the eTICI score in the following subgroups:

1. IV Alteplase use on admission (yes versus no)
2. MT started within 7.3h of symptoms onset versus MT started between 7.4h and 24h.
3. Admission serum glucose concentration≤100 mg/dL versus >100 mg/dL
4. Males vs. Females

3.5.5.Safety outcomes

1. Mortality at 90 days
2. sICH rates at 24 hours.

All ICH will be classified by a central core-lab using the ECASS3 criteria. Symptomatic ICH will be defined as per the ECASS3 definition: deterioration in NIHSS score of ≥4 points within 24 hours from treatment and evidence of any apparently extravascular blood in the brain in the 24 hours follow-up imaging scans. The incidence of any asymptomatic hemorrhage measured at 24 hours will also be compared.

3.5.6 Adverse events (AEs) and Serious Adverse Events (SAEs)

3.5.6.1 Definitions and Classification

An **Adverse Event** (AE) is any untoward medical occurrence in a patient temporarily associated with the use of the investigational drug, whether or not considered related to the investigational drug. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the drug, whether or not considered related to the drug.

Any AE experienced by the study subject after enrolment (equal to the time of randomization) must be recorded in the CRF.

All AEs and SAEs will be monitored and collected from the **time of enrolment** (defined as **time of randomization**) through 90 day follow-up visit. All SAEs and SUSAR must be reported to CRA or designee within 24 hours of becoming aware of their occurrence in order to comply with regulatory reporting requirements. In the event that the eCRF is unavailable a written form sent by e-mail or fax is acceptable (the required form will be filed in the ISF)

Underlying (pre-existing) symptoms or diseases are not reported as Adverse Events (AEs) unless there is an increase in severity or frequency during the course of the investigation, but they need to be reported in the eCRF as Relevant Medical History.
Death should not be recorded as an adverse event, but should only be reflected as an outcome to another specific AE/SAE.
A qualified medical investigator must review all information available to determine the seriousness, causality, severity and outcome of the AE as well as to assess whether it meets the criteria for classification as a serious adverse event, which requires immediate notification to the sponsor or its designated representative.
All AEs and the treatment and follow-up required must be documented in the subject's medical records and in the eCRF.
A procedural complication may constitute an AE if it results in an untoward change from the subject's baseline health.

Serious Adverse Event (SAE) is defined as an adverse event that:
a) Led to a death, injury or permanent impairment to a body structure or a body function.
b) Led to a serious deterioration in health of the subject, that either resulted in:
- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- In-patient hospitalization or prolongation of existing hospitalization, or
- In medical or surgical intervention to prevent life threatening illness

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.
Abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. ECG, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE as previously defined. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.
However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

3.5.6.2 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE into the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the appropriate AE/SAE CRF pages and forms. For each adverse event, start and stop

dates, action taken, outcome, intensity and relationship to study drug (causality) must be documented. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the CRF.
The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented. All details of any treatments initiated due to the adverse event should be recorded in the subject's notes and the CRF/form.

3.5.6.3 Prompt Reporting of SAEs

SAEs require immediate action. Once an investigator becomes aware that an SAE has occurred, he/she will immediately notify the clinical coordinator via telephone within one working day. The study SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee), and reported into the eCRF or to the study manager, within one working day of first becoming aware of the event. The equivalent SAE page should be filled in on the CRF.
If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event and completing the form. The form will be updated when additional information is received.
The investigator will always provide an assessment of causality at the time of the initial report. In accordance with local IEC requirements, the investigator must also notify their Ethics Committee of any SAEs according the guidelines of the Ethics Committee. The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgment of the likely causative factors.
This may include seeking further opinion from a specialist in the field of the adverse event or requesting extra tests. If a subject dies, any post-mortem findings, including histopathology will be provided if available. No medical help, diagnosis, or advice should be withheld from the subject due to an inability to contact the study manager/medical monitor.
When entered a SAE into the eCRF, an alert will be received by the designed persons (i.e.: monitor)

3.5.6.4 Evaluating AEs and SAEs

3.5.6.4 .1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF or SAE form should be assigned to one of the following categories:

Mild	Awareness of sign, symptom, or event, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity and may warrant intervention
Severe	Incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as previously described in Section **3.5.7.1 Definitions** and Classification.

3.5.6.4.2 Assessment of Causality

The Principal Investigator or a medically-qualified designee must assess the relationship between investigational drug and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational drug administration will be considered and investigated. The investigator will also consult the study drug information in the determination of his/her assessment. The causal relationship to the study drug assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

Unrelated	No temporal association, or the cause of the event has been identified, and the event determined to be due to a concurrent illness or effect of another drug reaction and is not related to the study drug.
Possibly related	Temporal association, but other aetiologies are likely to be the cause; however, involvement of the study drug cannot be excluded based on available information
Probably related	Temporal association and there is no other reasonable medical explanation for the event based on available information

3.5.6.4.3 Assessment of Expectedness

Expected adverse reaction, the nature or severity of which is consistent with the applicable study drug information (e.g. Investigators' Brochure) for an unapproved medicinal product).
Unexpected adverse reaction, the nature or severity of which is not consistent with information in the study drug information.

3.5.6.4.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to actively follow each subject and provide further information into the eCRF pertinent forms on the subject's condition. All AEs and SAEs documented at a previous visit/contact and are designated as on-going, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, or consultation with other health care professionals. New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator.

3.6 Statistical methods

3.6.1 General Remarks

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP / ICH / 363/96)[49]. A detailed Statistical Analysis Plan (SAP)[50] agreed upon by the sponsor and the Project Statistician will be available before the un-blinding of the data base. This SAP will follow the general regulatory recommendations given in the ICHE9 [51] guidance, as well as other specific guidance on methodological and statistical issues[52]. Also, it will stick to the recommendations given by the consensus documents of the scientific journals[53,54,55] to improve reliability and value of medical research literature by promoting transparent and accurate reporting of clinical research studies.
The SAS System[56] (Release 9.4, or an upgraded version), or equivalent validated statistical software, will be the statistical software used to analyze the data sets.
A summary of the overall approach to statistical analysis is presented hereafter.

3.6.2 Sample size calculation

A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least 80% statistical power for the primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm (odds ratio (OR) of 2.33) for a 5% two-sided type I error. This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56%. Study losses are not taken into account as all randomized patients exposed to the IMP will be included in the analysis. The number of randomized patients not exposed to the IMP is expected to be negligible.

3.6.3 Data Blind Review (DBR)

The Data Blind Review (DBR) will be performed before lock of database. Data will be examined for compliance with the trial protocol by the monitor and the data manager. Deviations will be sent to the project statistician to plan listings for the Data Blind Review (DBR). The objective is to carry out the population selection and definition of the final study populations as well as a preliminary assessment of the quality of the trial data.

3.6.4 Analysis populations

There will the following analysis populations for this study:
1) Full Analysis Set (FAS): All patients who are randomized into the study regardless of any treatment of protocol violation, fully in accordance with the intention-to-treat (ITT) principle.
2) Modified Full Analysis Set (mFAS): All patients who are randomized into the study and who have received the investigational medicinal product (IMP) will be included in the mFAS population.
3) Per Protocol Population: Per protocol (PP) patient sets will be defined as those patients included in the mFAS set without major protocol deviations that might impact the study's main assessments. These deviations will be assessed during the data review prior to database lock.
4) The Safety population (SP) is defined as all randomized participants who received the investigational drug (any of the two-arms treatment). In this study the SP will have the same

definition than the mFAS subset and thus, all safety analyses will be conducted on the mFAS population.
The precise reasons for excluding participants from each population will be fully defined and documented independently of the randomization codes during the Data Blind Review and before the database lock.

3.6.5 Randomisation Procedure

Randomisation codes were produced by means of the PROC PLAN of the SAS system, with a 1:1 ratio of assignment between both arms, stratifying by centre, and use of IV alteplase (no or yes), in blocks multiple of 2 elements. The codes will released to the manufacturer site, which is independent from the study sponsor and be managed from the eCRF in a blinded manner.

3.6.6 Inferential Analysis

No inferential analysis will be performed for the baseline comparability. The inferential analyses will be limited to the efficacy variables, and the adverse events. For adverse events the following criteria is predefined: bleeding events (major, minor, overall), organ-system according to the MedDRA codes, and the MedDRA preferred-terms with at least 10% overall prevalence or at least the 5 more prevalent preferred-terms.

3.6.6.1 Primary endpoint

The proportion of patients with a mRS 0 to 1 at 90 days will be estimated using a log-binomial regression model including the stratification variables, except centre. In the unexpected event that the model does not fit, the Poisson regression model with long-link and robust variance estimator will be used instead[57,58,59,60,61].

3.6.6.2 Secondary endpoints and safety outcomes

Binary outcomes

Binary efficacy and safety (mortality at 90 days and sICH rates at 24 hours) outcomes will be analysed as described for the primary endpoint.

Shift outcomes

The shift analysis of the modified Rankin Scale (mRS) will be analyzed using the proportional odds model[62], combining into single worst rank the last two categories (5: severe incapacity and 6: death) and the stratification variables except centre. The common odds ratio can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study[63,64,65]. The stratified non-parametric van Elteren test[66], using modified ridit scores which is as a direct extension of the extension of the Wilcoxon's rank-sum test for 2-samples, will be calculated as a sensitivity analysis to compare the modified Rankin scale as an ordinal rather than a binary outcome, without assuming proportional odds[67,68].

The median of the absolute values the 95% confidence interval (95%CI) will calculated using the Hodges-Lehmann methods (i.e. median of all cross differences between treatments based on the Mann-Whitney distribution)[69,70].

Continuous outcomes

Continuous variables will be analyzed using Mixed Models[71], including in the model the baseline measurement, the stratification variables except centre, treatment as well as the interaction between treatment and time, declaring time as categorical. The variance-covariance matrix will be fixed initially as unstructured. If this analysis fails to converge, the following structures will be tested in the following order until convergence: AR(1) (Auto-Regressive first order), Toeplitz and CS (Compound Symmetry). Contrasts between dialysis groups will be performed by time-point. The treatment effect will be estimated through adjusted means –Least Square Means (LSMeans) – its standard error – Standard Error of Mean (SEM)- and its 95%CI. Differences between treatments will be estimated through the differences between LSMeans, SEM and 95%CI.

3.6.6.3 General strategy for the rest of variables

The rest of variables will be analyzed according to the following strategy: the Fisher's exact test to compare categorical variables, the dependent or independent t-test for continuous Gaussian-distributed variables and the Mann-Whitney for ordinal and non-Gaussian continuous data. The survival function for death as well as the median [95% confidence interval -95%CI-] will be estimated by means of the Kaplan-Meier method. Group comparisons will be conducted using the stratified the log-rank test and, hazard ratios -HR- (95%CI) were taken from the Cox model[72].

3.6.7 Multiplicity adjustments and interim analysis

The analysis will follow the principles specified in the ICHE9[73] and the CPMP/EWP/908/99[74] Points to Consider on Multiplicity issues in Clinical Trials guidelines.
No interim analysis is planned for this study. For this reason, there is no statistical criterion for early termination of the trial.

3.6.8 Handling of missing data

The handling of missing data will follow the principles specified in the ICH-E9[32] and the CPMP/EWP/1776/99 Rev1. Guideline on Missing Data in confirmatory trials Guidelines[75].
Missing data on the primary outcome or other binary efficacy secondary outcomes will be considered as failures, irrespectively to the reason for missingness. For mRS the worst case imputation will be used (i.e. imputing the worst category of the scale). With regards to the continuous variables, mixed models[76,77,78] are robust to the presence of missing at random (MAR) and conducts the analysis with all participants despite the presence of missingness. Of note, this method calculates the estimations based on the variance-covariance structure but without any formal imputations.

No formal imputations will be performed for the rest of variables and the analyses will be based on the Available Data Only (ADO) approach.

3.6.9 Subgroup analysis

The following 5 subgroups are declared of special interest and they will be investigated for the proportion of patients with improved mTICI 2b score:

- IV Alteplase use on admission (yes versus no)
- MT started within 7.3h of symptoms onset versus MT started between 7.4h and 24h.
- Admission serum glucose concentration $\leq$100 mg/dL versus >100 mg/dL
- Males vs. Females
- Baseline angiographic score 2b brain reperfusion versus baseline angiographic score eTICI2c/3 brain reperfusion

No other subgroup analyses are planned. In case of any post-hoc subgroup analysis, they will be justified and identified as data-driven and, they will follow the principles and regulatory recommendations[79].

The following strategy will be conducted before splitting the analysis into subgroups:

1. Test of the overall treatment effect
2. Test of the treatment-by-subgroup interaction at the 10% level of significance
3. Test of the treatment effect in each subgroup category

If the three criteria are met, then the subgroup analysis will be given the maximal level of evidence for this analysis. However, this subgroup analysis is predefined as exploratory and the interpretation should be taken with caution. If any of the criterion are not meet, the chances of type I error increase are higher and this will have an impact in the interpretation.

3.7 Study feasibility

The sites participating in CHOICE performed in 2016 575 MT procedures that were registered in the *Sistema Online d'Informació de l'Ictus Agut* (SONIIA) Registry. For pooled data analysis of five RCTs of MT reported an average rate of 38% of mTICI2b score and an average rate of 59% of mTICI3 score at the end of MT. These figures allow estimating that the total potential annual accrual rate at the participating sites is sufficient to terminate the trial within the allotted recruitment duration of 24 months.

4. DATA MANAGEMENT / MONITORING AND QUALITY CONTROL

4.1 Data collection methods

An electronic Case Report Form (eCRF) will be completed for each study subject, summarizing all clinical screening and study data. Subjects will only be referred to in the eCRF by their subject number and initials in order to retain subject confidentiality.

4.2 Data management

Data will be captured in an eCRF and the Investigator is responsible for ensuring the prompt and accurate reporting of study data into the eCRF. The eCRF is reachable via the internet at any time. The system uses a secured data connection (with Secure-Sockets-Layer protocol, SSL) to transfer the data from the study centres to the central database. Data management documentation will be prepared by the Medical Statistics CRO in charge of the eCRF and data management.
The data collection will be monitored by external qualified staff and entered into a remote access database (electronic Case Record Form eCRF). The eCRF will be managed by the IDIBAPS. This system will meet the general[80] and specific[81] standards of Good Clinical Practice and the highest requirements of computer validation[82,83,84,85], with restricted user-level access, equipped with filters to detect inconsistencies and traceability of all information to closure end thereof. Any data transfer will be done using secure SSL connection with encryption. Export for archiving of the clinical database including audit trails in hard- and software independent storage formats will be provided by IDIBAPS.

Furthermore, the technical support will be provided for the study centers during the study duration (administration of logins, roles and rights).

In case of scheduled, unscheduled analyses or other needed reports the data will be exported from the database. In a further process these data will be checked, prepared and delivered for these purposes.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the sponsor and the Medical Statistics core facility and with a sound justification and full traceability of the process.

At the end of the study the entire database will be exported. The final data management process contains the plausibility, consistency and range checks of the data. The missing data will be identified as well. Data Clarification Forms will be generated for data clarification.

After all data management processes are completed, the cleaned data will be available for the statistical analysis. The final data will be delivered in a defined SAS data format, including a data management report as well.

4.3 Data monitoring

Study monitoring will be performed by ANAGRAM-ESIC. Best conduct of the study will be ensured through frequent contacts by phone and in person with the responsible Investigator, in accordance with ANAGRAM-ESIC Standard Operating Procedures, with the purpose of facilitating the work and fulfilling the objectives of the study. Site visits will enable the Monitor to maintain current, personal knowledge of the study through review of the records, comparison with source documents, and observation and discussion of the conduct of the study with the Investigator. The Monitor is responsible for monitoring adherence to the Protocol and completion of the eCRF. They are also responsible for the organization, monitoring, supply of study materials and quality assurance of the study.

In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Study Monitor and Regulatory Authorities is mandatory.

The trial will be managed by a Steering Committee, with Chair, Ángel Chamorro. There will also be an independent Data Safety Monitoring Board (DSMB) –- chaired by Tudor Jovin. The Steering Committee comprising investigators from each participating centre and a Neurointerventional Committee, with Chair Jordi Blasco, will comprise neurointerventionalists from each participating centre. A Neuroimaging Core Lab with Chair Luis San Román, will manage all the imaging data collected in the trial. A Patient's recruitment Board with Chair Monica Millán will supervise that patient's accrual in the trial abide to anticipated estimations.

4.4 Screening log and Codi Ictus Catalonia (CICAT)

Each collaborating site is requested to complete a screening log of all patients treated with mechanical thrombectomy who are not included in the trial. The log is used to monitor recruitment and identify barriers to recruitment at that site. Further, data from the CICAT registry, a government-mandated, prospective, hospital-based dataset will also be used to cross-check the information reported in the screening logs. Indeed, CICAT reports prospectively all Stroke Code activations in Catalonia, and capture information about the presence of LVO (TICA, MCA M1 or M2, tandem or basilar occlusion) and revascularization treatments used.

4.5 Data auditing

The Steering Committee has assigned a CRO to this study whose duties are to aid the P.I. and the Steering Committee members in the maintenance of complete, legible, well organized, and easily retrievable data. Personnel from CRO will ensure that the study complies with relevant Good Clinical Practices (GCPs). Periodic monitoring visits will be made throughout the investigation to assure that the investigator's obligations are being fulfilled. Monitoring visits will be performed to verify data accuracy and ensure queries are resolved.

4.6 Independent Committees

- Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board will be established. The purpose of the DSMB is to review, on a regular basis, accumulating data from the on-going trial. The DSMB will be composed of two stroke neurologists and a statistician who are not participating in the study and are not affiliated with the sponsor. The role of the DSMB will be to: 1/Review the occurrence of AEs and 2/ Make recommendations to the Executive Committee regarding safety of the study. A strict control of predefined AEs and SAEs will be ensured through monitoring by the CRO.

A Data Safety Monitoring Board (DSMB) wills follow-up the safety of the study. Although the DSMB will review data in a blinded manner (Group A and B), the date of the SAP closure will be set before the first unblinded review so that the study will maintain the integrity and will avoid any operational bias. Any potential analysis amendment will be traced and justified, if applicable. The study followed the regulatory recommendations regarding the functions and procedures of these committees[86].

- *Independent Imaging Core Lab (ICL)*

An independent Imaging Core Lab will be established. The purpose of the ICL is to review, on a regular basis, accumulating imaging data from the on-going trial. The ICL will be composed of two neuro-radiologists, a stroke neurologist and one physicist. The role of the DSMB will be to: 1/Review the occurrence of AEs and 2/ Make recommendations to the Executive Committee regarding safety of the study. A strict control of predefined AEs and SAEs will be ensured through monitoring by the CRO.

4.7 Training of investigators and site personnel

The training of the Investigator, and appropriate clinical site personnel will be the responsibility of the Study Coordinating Group and may be conducted during local investigator meeting, a site initiation visit, or other appropriate training sessions. Training will include, but not be limited to, the study protocol, eCRF completion, neurological scale evaluation and site personnel responsibilities. All Investigators and site personnel that are trained must have their training documented.

Prior to the initiation of the study and subject enrolment, the Study Coordinating Group or designee will visit each site where the trial is conducted. The Sponsor or designee will ensure that the site personnel are informed about and understand the clinical study requirements.

Specific training will be offered to research team professionals.

5. ETHICS AND DISSEMINATION

5.1 Research Ethics approval

Clinical Research Ethics Committee of the hospital Clínic, which will act as the CEIm for this research project and approve Study Protocol and the patient information sheet and informed consent form, as applicable to this type of regulation studies. The Clinical Research Ethics Committee will also approve any revision or modification of the research protocol, the informed consent form or the patient information sheet.

This study will be conducted according to the provisions of the RD 1090/2015 of December 4, which regulates clinical drug trials, the Royal Legislative Decree 1/2015 of July 24, Law on guarantees and rational use of medicines and medical devices, the Royal Decree 577/2013 of 26 July, which regulates pharmaco-surveillance and, all in what is applicable to them, and the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and good clinical practice guidelines.

The trial will be conducted in agreement with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

5.2 Consent

Patient or his/her representative will sign the specific approved version of informed consent form at hospital arrival before participating in the clinical trial and inclusion of its clinical data into the electronic CRF.
A signed informed consent, indicating full and complete understanding of the study, should be obtained prior to initiating the randomization process or any study procedures, unless the site has been granted an explicit waiver of consent or allowance for verbal consent from the CEIm. This specific allowance of verbal consent will be requested by a telephone call in presence of a waiver (neurologists) for patients that are transferred from other centers without accompanying relatives in the ambulance, in order to not delay patient's allocation.
Given the characteristics of the study that will be carried out in the context of an emergency situation, the basic ethical principles: autonomy, beneficence, non-maleficence and justice have been taken into consideration:
- Beneficence and non-maleficence are fully respected, being both alternatives according to the best treatment criteria.
- Patients' autonomy is respected to make their own decisions regarding their subsequent monitoring.
- Distributive justice is respected since the study is equally based on all patients who meet the selection criteria and excludes differences based on social or economic levels/ conditions.

Written Informed Consent must be given after the context of the study has been fully explained in a language that is easily understood by the subject or his/her representative. The subject or his/her representative must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.
Written Informed Consent must be recorded appropriately by means of the subject's, or his/her representative dated signature. The consent process must be documented in the subject's medical chart.

5.3 Confidentiality

Investigators, who use information about the health of their research participants, are required except in specific circumstances, to get written permission to use their participant's protected health information (PHI) for the research study. Each participating clinical center is expected to comply with its individual performance site's requirements established for compliance of the local confidentiality policies.
All study data will be collected in an anonymous way, through the eCRF and no personal data will be extracted from investigational sites in any case.

5.4 Record Retention

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Documents must be retained for at least 25 years as per Spanish and European guidelines.

The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Sponsor must receive written notification of this custodial change.

5.5 Dissemination policy

A writing committee will be formed to review and publish the data from the study. This committee will consist of the Steering Committee and a subset of investigators. The writing committee will write/review all drafts of abstracts and full-length manuscripts and will choose the appropriate journal (for manuscripts) or meeting (for abstracts) for submission.

The CHOICE Steering Committee commits that when the study is completed, the data from this study will be published within 3 months, regardless of the outcome of the study and the trial will be listed on the clinical trials website.

All information concerning the CHOICE trial supplied to the investigators by the Steering Committee and not previously published is considered confidential and shall remain the sole property of the CHOICE Steering Committee. The investigator agrees to use this information only in accomplishing the study and will not use it or the data generated from the study for other purposes without first obtaining written authorization from CHOICE Steering Committee.

It is understood that CHOICE Steering Committee may disclose this information as required to other CHOICE clinical investigators or to government regulatory agencies. The investigator understands that she or he has the obligation to provide complete test results and all data collected during this study to the Steering Committee.

6. APPENDICES

6.1 Abbreviations and Acronyms

AE	Adverse Event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios
AHA/ASA	American Heart Association/American Stroke Association AMI Acute Myocardial Infarction
ASPECTS	Alberta Stroke Program Early CT score
CICAT	Codi Ictus Catalonia
CRF	Case Report Form
CT	Computerized Axial Tomography
CTA	Computerized Axial Tomography Angiography
CTP	Computerized Tomography Perfusion
CRO	Contract Research Organization
EMS	Emergency Management of Stroke
eTICI	expanded Treatment In Cerebral Infarction
GCP	Good Clinical Practice
IA	Intra-arterial
ICA	Internal Carotid Artery
ICH	Intra-cerebral Hemorrhage
IMS III	Interventional Management of Stroke Trial III
INR	International Normalized Ratio
ISF	Investigator's Site Folder
IV	Intravenous
IVT	Intravenous Thrombolysis
LVO	Large Vessel Occlusion
MAR	Missing at random
MCA	Middle Cerebral Artery
MCD	Mechanical Clot Disruption
mFAS	Modified Full Analysis Set
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scale
MT	Mechanical thrombectomy
mTICI	Modified Treatment In Cerebral Infarction scale
M1	Proximal segment of the MCA from the origin to bifurcation/trifurcation, also known as horizontal or sphenoidal segment
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio

PCI	Percutaneous Coronary Intervention
Pp	Per Protocol
PROBE	Prospective randomized open blinded end-point
RACE	Rapid Arterial oCclusion Evaluation
RCT	Randomized controlled trial
RD	Royal Decree
rt-PA	Recombinant tissue Plasminogen Activator
SAE	Serious Adverse Event
SICH	Symptomatic Intra-Cerebral Hemorrhage
SONIIA	Sistema ONline d'Informació de l'Ictus Agut
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterilized Water for Injection

6.2 INFORMED CONSENT

ATTACHED AS A SEPARATE DOCUMENT

6.3 Modified Rankin scale

Modified Rankin Scale-Structured Interview (MRS-SI)

0 = No symptoms at all; no limitations and no symptoms.

1 = No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?

2 = Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?

3 = Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?

4 = Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?

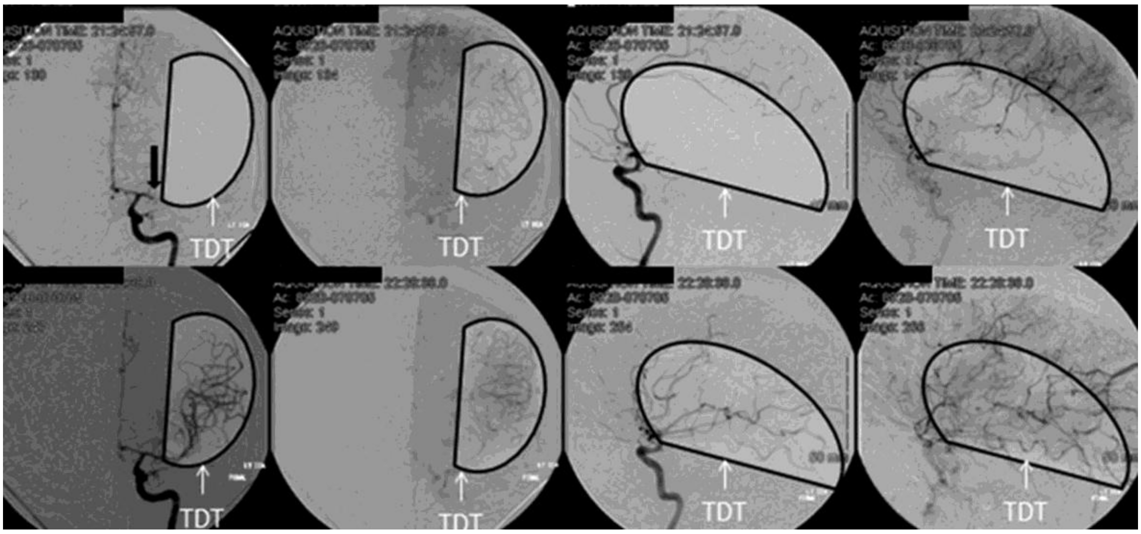
5 = Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?

*Wilson, L. J. T., Harendran, A., Grant, M., Baird, T., Schultz, U. G. R., Muir, K. W., Bone, I. (2002). Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the Modified Rankin Scale. *Stroke*, 33, 2243-2246.

6.4 Angiographic assessment: The mTICI score

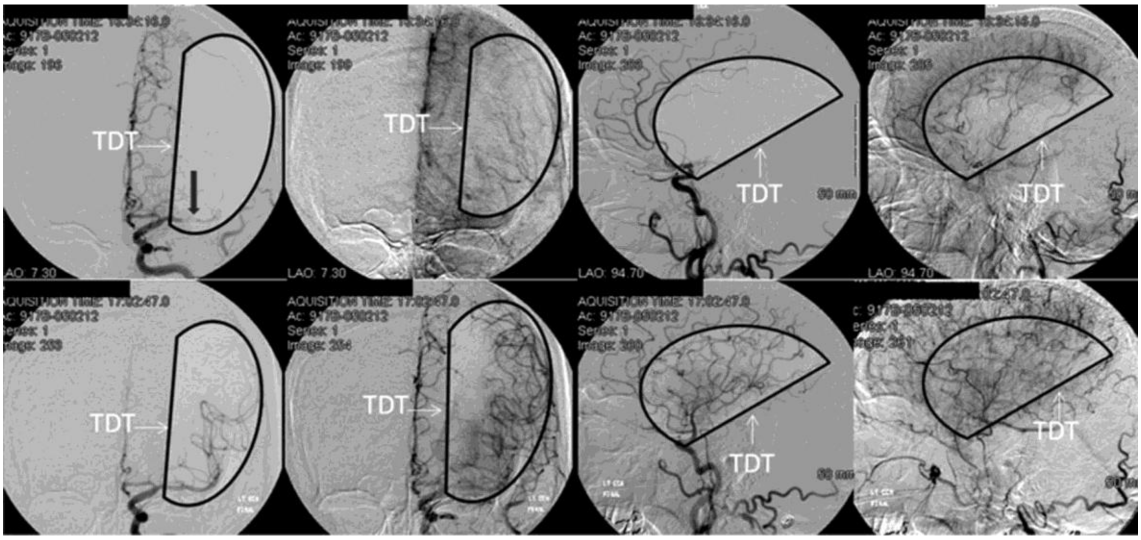
The Thrombolysis in Cerebral Infarction (TICI) scale was originally proposed in a position statement that attempted to standardize clinical trial design and reporting for IAT.[87,88].The TICI scale specifically addresses the extent of tissue reperfusion, as represented by the capillary blush on DSA. TICI is graded by visually estimating how much of the initial antegrade capillary blush defect (or target downstream territory [TDT] is reperfused (numerator). The TICI scale distinguishes no perfusion (TICI grade 0; Figure 2), minimal flow past the occlusion but no perfusion (grade 1; Figure 3), minor partial reperfusion (grades 2a; Figures 4 and 5), major partial reperfusion (2b; Figure 2), and complete reperfusion without any flow defects (grade 3; Figures 3 and 4). The original TICI system defined TICI 2b as restoration of more than two thirds of the TDT. This is in contrast to the subsequent modification (modified treatment in cerebral ischemia [mTICI]) introduced by the IMS investigators, which uses a threshold of more than half of the TDT.[89] The advantage of mTICI is its simplicity (ease of visually estimating 1/2 versus 2/3 reperfusion), and previous work has demonstrated excellent inter-rater agreement for distinguishing <50% versus ≥50% reperfusion of the downstream territory.[90]

Fig 2



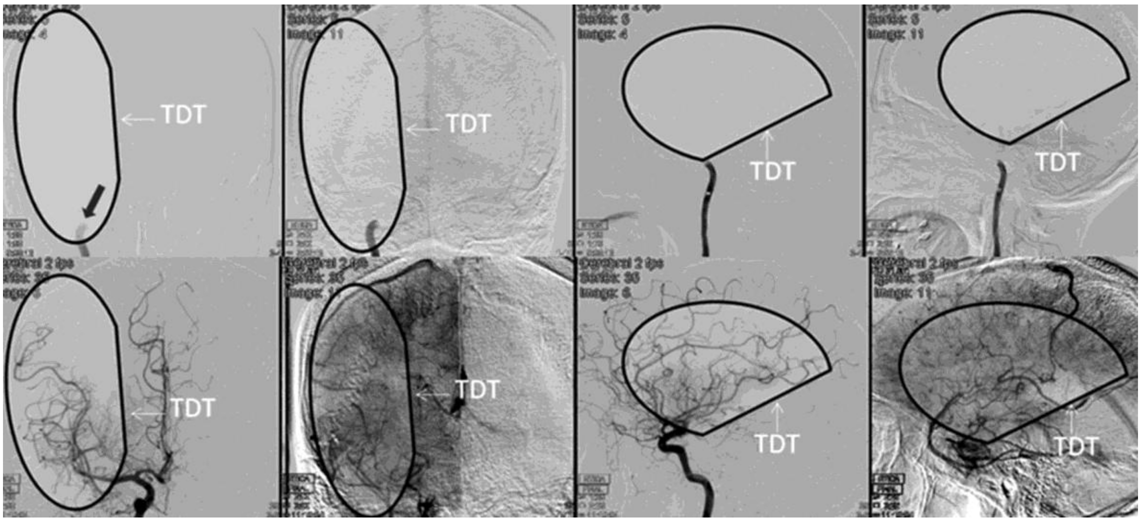
Top, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2b after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).

Fig 3



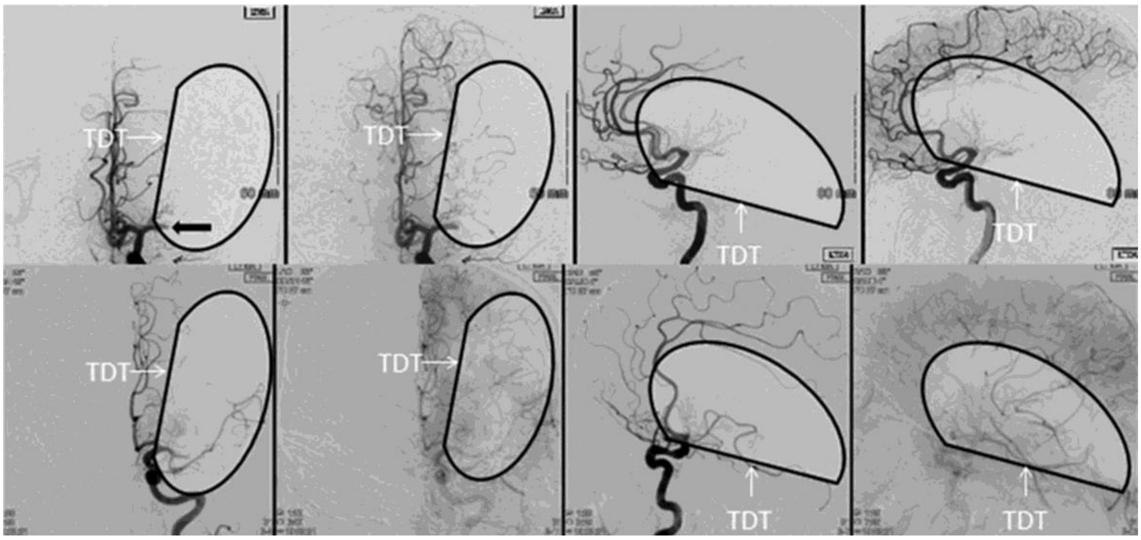
Top, Anteroposterior (**left**) and lateral (**right**) in an early arterial and late capillary phases depicting TICI 1 at baseline. **Bottom**, Same phases depicting TICI 3 after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL). Ischemic arteriovenous shunting is noted with opacification of straight sinus (**right bottom** corner).

Fig 4



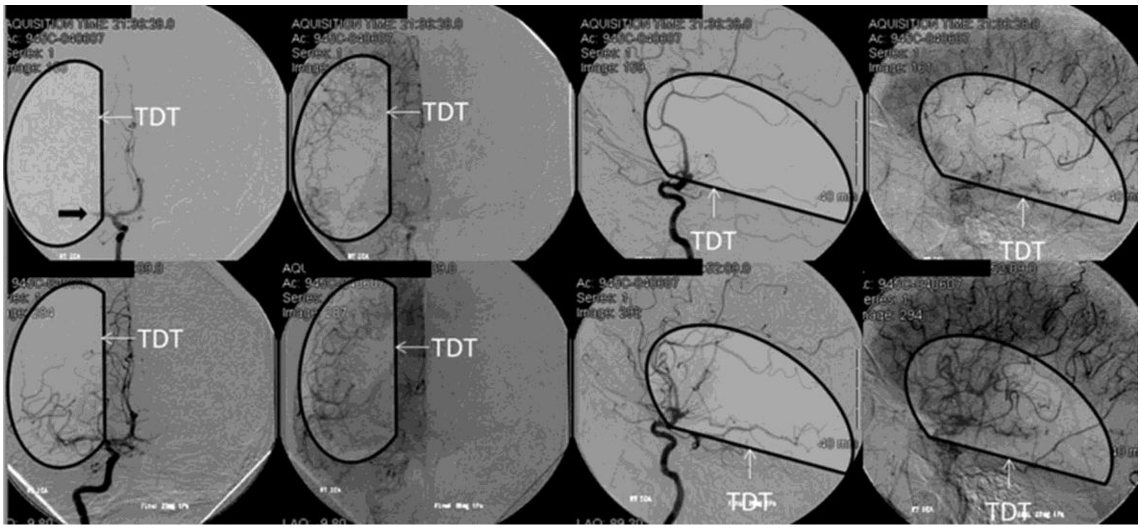
Top, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting thrombolysis in cerebral infarction (TICI) 0 at baseline. **Bottom**, Same phases depicting TICI 3 after IAT. Black arrow indicating the target arterial lesion (TAL): Distal ICA proximal to the ophthalmic artery. Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL). Early ischemic arteriovenous shunting is noted in the right lower corner.

Fig 5



Top, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2a after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).

Fig 6



Top, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2a after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).

6.5 Study assessments

Assessments	Baseline information	Procedure/ Allocation	Follow up 24h (-/+12h) post-randomization	Follow up 48h (-/+ 24h) post-randomization	Follow up 5 days (±2 d) post-random, or discharge (whatever occurs first)	Follow up 90 days (± 14 d) post-random
Admission Details	X					
Demographics	X					
Medical History	X					
Eligibility Criteria		X				
Informed Consent	X					
Randomization		X				
Blood test *Including INR*	X					
mRS	X[1]				₵	₵
NIHSS assessment	X		₵	₵	₵	₵
NCCT / MRI	X		X			
CT-P/ DWI-MRI	X					
Angiogram		X				
Blinded Study medication administration		X				
Post-MT angiography		X (if applicable)				
MRI (DWI/T2 sequences) *Or NCCT if MRI not possible*				X		
Stroke etiology						X
Procedure Details		X				
Barthel Scale						X
EuroQol EQ-5D						X
(S) AEs	.....on an ongoing basis.....					
Relevant Meds	X	X	X	X	X	

[1] This mRS score should be based on subject's score prior to the stroke symptom onset.
₵ To be done by an accredited local evaluator

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