Study Protocol

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Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke (CASES) study protocol for a multicenter randomized clinical trial

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Abstract

Background: The optimal acute management of patients with acute ischemic stroke and a tandem lesion, defined as intracranial large vessel occlusion (LVO) with concomitant carotid artery stenosis or occlusion, remains unclear. Our aim is to assess the efficacy and safety of immediate carotid artery stenting (CAS) compared to delayed management in patients undergoing endovascular treatment (EVT) for acute ischemic stroke due to tandem lesions.

Study design: CASES is a phase 3 multicenter prospective randomized open-label blinded endpoint (PROBE) non-inferiority clinical trial. Patients with a computed tomography angiography proven intracranial LVO in the anterior circulation and ipsilateral proximal carotid artery stenosis (⩾50%) or occlusion of presumed atherosclerotic origin will be randomized to either immediate CAS during EVT or to EVT followed by a deferred strategy, which may include carotid endarterectomy (CEA), CAS, or medical management. CASES will be conducted in 27 EVT centers in Belgium and the Netherlands. A total of 600 patients will be included.

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Study outcomes: The primary outcome is the score on the modified Rankin Scale (mRS) at 90 days. Secondary outcomes include excellent (mRS 0–1) and good (mRS 0–2) functional outcome at 90 days, stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 h and 5–7 days, recanalization, infarct volume at 24 h, ischemic stroke recurrence, carotid artery re-occlusion, symptomatic intracranial hemorrhage, and mortality.
Summary: This study will provide high-quality randomized data on the efficacy and safety of immediate CAS in patients undergoing EVT for acute ischemic stroke due to a tandem lesion.
Trial registration: ClinicalTrials.gov NCT06511089; ISRCTN 14956654

Keywords
Ischemic stroke, endovascular treatment, carotid stenting, randomized controlled trial, protocol

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Introduction and rationale

Tandem lesions, defined by the combination of an intracranial large vessel thrombo-embolic occlusion (LVO) and a ⩾50% stenosis or occlusion of the ipsilateral proximal internal carotid artery (ICA), are seen in approximately 20% of patients undergoing endovascular treatment (EVT) for acute ischemic stroke.[1] Approximately 60% to 70% of tandem lesions are caused by atherosclerotic plaques, 20% to 30% by dissections, with the remainder resulting from isolated (floating) thrombi without associated high-grade atherosclerotic stenosis, and, more rarely, from radiotherapy induced stenosis, immune-mediated arteritis, or carotid webs.[2]

Acute ischemic stroke in patients with tandem lesions often leads to poor functional outcome without treatment.[3] EVT of intracranial LVOs in patients with tandem lesions clearly improves outcome with a treatment effect comparable to that of patients with isolated intracranial occlusions.[4] However, the best treatment strategy to manage the proximal atherosclerotic lesion in the ICA during EVT remains unknown.[5] European guidelines recommend considering carotid endarterectomy (CEA) or carotid artery stenting (CAS) in patients with transient ischemic attack (TIA) or non-disabling stroke caused by ⩾50% stenosis of the ICA within 2 weeks of the initial event to prevent a recurrent event. These recommendations are based on secondary prevention trials comparing CEA versus medical management and CEA versus CAS in patients with TIA or non-disabling stroke, but no trials have been performed including patients with LVO.[6,7] However, from a patient perspective, immediate CAS during EVT might be a preferred strategy because a deferred carotid revascularization procedure with CEA or CAS can be avoided in the days/weeks following stroke onset. An additional advantage of immediate CAS is the immediate prevention of recurrent stroke from the atherosclerotic plaque. Several large observational registries and meta-analyses suggest that immediate CAS in patients with tandem occlusions is safe during EVT, with higher reperfusion rates and improved functional outcome, and no significant increase in the incidence of symptomatic intracranial hemorrhage.[1,8–12] These results should be interpreted with caution due to the non-randomized design and potential selection bias in these studies, hence the efficacy and safety of immediate CAS during EVT in patients with tandem lesions remain mostly unknown. There is a clear and urgent need for an adequately powered randomized clinical trial (RCT) to address this critical clinical question.

The Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke (CASES) trial will compare the efficacy and safety of two treatment strategies in patients undergoing EVT for acute ischemic stroke due to an ipsilateral tandem lesion of presumed atherosclerotic origin.

Methods

Study design

This is a phase 3 international multicenter prospective randomized open-label blinded outcome assessment (PROBE) non-inferiority trial. Patients with acute ischemic stroke and computed tomography angiography (CTA)-proven intracranial LVO in the anterior circulation (ICA, M1 or M2) and ipsilateral proximal ICA occlusion or stenosis of 50% or more of presumed atherosclerotic origin, who are eligible for EVT according to guidelines, will be included. Patients will be randomized to either immediate CAS during EVT or to a deferred treatment strategy (CEA, CAS or best medical management alone, according to the judgment of the treating physician).

The trial will be performed in comprehensive stroke centers that perform EVT in the Netherlands (17 centers) and Belgium (10 centers). The CASES trial is embedded in the Collaboration for New Treatments of Acute Stroke (CONTRAST 2.0) consortium, a collaboration of clinical

Table 1. Inclusion and exclusion criteria.

Inclusion criteria:
- Acute ischemic stroke due to proximal intracranial occlusion in the anterior circulation (intracranial ICA, M1, proximal M2) on CTA
- Stenosis ⩾ 50% according to the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) criteria[13] or acute occlusion of the ipsilateral cervical carotid artery of presumed atherosclerotic origin on baseline CTA or first DSA run of the common carotid artery
- Eligible for EVT according to the guidelines: EVT within 6 h of onset or EVT between 6 and 24 h of onset based on perfusion CT imaging selection (conform local guidelines)
- Baseline National Institutes of Health Stroke Scale (NIHSS) score ⩾ 2
- Age >18 years
- Written informed consent (deferred consent)

Exclusion criteria:
- Any intracranial hemorrhage
- Cervical carotid artery stenosis or occlusion due to causes other than presumed atherosclerosis (e.g. carotid artery dissection, floating thrombus, carotid web)
- Any exclusion criterion for EVT according to the guidelines
- Pre-stroke disability (defined as a modified Rankin Scale score >2)
- Gastrointestinal or urinary tract hemorrhage in the preceding 6 weeks
- Severe head trauma within the preceding 6 weeks
- Recent infarction on baseline brain CT in the same vascular territory within the preceding 6 weeks
- Known allergy to aspirin and/or clopidogrel
- Pregnancy
- Participation in another randomized controlled intervention (EVT) trial
- Alberta Stroke Program Early CT Score (ASPECTS[14]) < 6

and translational scientists focused on RCTs in stroke patients. The study is funded by ZonMw and the Belgian Health Care Knowledge Centre in the BeNeFIT (Belgium-Netherlands Funding of International Trials) program. The study is registered with ClinicalTrials.gov (Identifier: NCT06511089) and ISRCTN registry (ISRCTN14956654). Patient enrollment started in July 2023.

The study has a non-inferiority design, with the assumption that immediate CAS during EVT will become the new standard of care if it is proven to be non-inferior in terms of safety and efficacy compared to the deferred treatment.

Patient population

Table 1 lists the inclusion and exclusion criteria.

Randomization

Following verification of eligibility in all consecutive patients, patients will be randomized in a 1:1 ratio by the treating physician before initiating EVT, based on the CTA findings. In case of significant doubt on the CTA regarding the presence of carotid stenosis/occlusion of atherosclerotic origin or pseudo-occlusion, randomization can also take place after the first angiographic run of the common carotid artery, confirming a cervical stenosis of ⩾50% or complete occlusion due to atherosclerosis. Randomization will be performed by a computer and web-based procedure, using permuted blocks, and is stratified by center.

Deferred consent procedure

The medical ethical committee approved the use of deferred consent, recognizing that the CASES trial involves the investigation of an acute intervention in an emergency setting for a life-threatening disorder. The investigators will obtain written consent from all patients or their representative after the endovascular procedure. The patient or legal representative will be asked for consent by trained research personnel as early as deemed appropriate and reasonable after hospital admission. If a patient or his/her representative refuses to provide consent, participation in the trial will be terminated immediately. However, their data will be used in a strictly anonymized form to obtain data on serious adverse events (SAE), symptomatic intracranial hemorrhage (sICH) and mortality for the purpose of safety analyses to accurately describe the group without consent. For every patient that withdraws consent, an additional patient will be included. The patient or representative may – at any given time – withdraw informed consent without explanation. When consent by proxy has been obtained and the patient recovers, we will again ask for written consent from the patient. In the event of a patient's death before obtaining deferred consent, the representative will be informed about trial participation.

Treatment or intervention

In patients allocated to the immediate CAS group, the ICA stenosis will be stented during EVT, before intracranial

Table 2. Study procedures.

Baseline	
Clinical assessment	Demographics, risk factors, medication, medical history, NIHSS, laboratory characteristics
Neuroimaging	Brain NCCT+CTA
Follow-up	
Clinical assessment at 24 h	NIHSS
Neuroimaging at 24 h (±12 h)	Brain NCCT+CTA
Clinical assessment at 5–7 days or at discharge	NIHSS
Clinical assessment at 90 days (±14 days)	Telephone interview (mRS+EQ-5D-5L)
Imaging at 90 days (±14 days)	Duplex ultrasound examination carotid artery

thrombus removal or directly after, at the discretion of the interventionalist. The use of periprocedural heparin and distal protection devices during CAS is discouraged. The patients allocated to the deferred strategy will not receive stenting during EVT. Percutaneous transluminal angioplasty (PTA) of the ICA stenosis is allowed. EVT will be performed with either stent retriever and/or thrombus aspiration catheters at the discretion of the interventionalist.

In patients allocated to the stenting group, we highly recommend a loading dose of 500 mg intravenous aspirin, just prior to or shortly after stenting, followed by an oral dose of 1×100 mg aspirin and 1×75 mg clopidogrel 24 h after the loading dose and after ruling out intracranial hemorrhage on follow-up brain CT.[15] Dual antiplatelet treatment is recommended for at least 3 months. Patients allocated to the deferred management will receive treatment with antiplatelet or antithrombotic therapy according to national or European guidelines. Thereafter, management can include CEA or CAS, preferably within 2 weeks of stroke onset, or best medical treatment without CEA or CAS, according to the current guidelines and depending on the functional recovery of the patient.

Study procedures

Patients will undergo assessment of stroke severity at baseline, at 24 h, and at 5–7 days with the National Institutes of Health Stroke Scale (NIHSS) score. All patients receive a non-contrast CT (NCCT) and CTA at baseline as well as a NCCT and CTA at 24h to assess infarct volume, intracranial hemorrhage, stent patency (or the degree of residual stenosis in the deferred treatment arm), and the degree of intracranial recanalization. Functional outcome will be assessed by the modified Rankin Scale (mRS) score and the quality of life with Euro-QoL 5 dimensions 5 levels (EQ-5D-5L) questionnaire after 90 days during a telephone interview. Furthermore, a duplex ultrasound of the ICA will be performed at 90 days. A complete overview of study procedures is listed in Table 2.

Outcomes

The primary endpoint is the mRS score at 90 days after stroke onset. The mRS score is a disability scale ranging from 0 (no symptoms at all) to 6 (death).[16]

The patient or the representative, and the treating physicians are aware of the treatment allocation. The mRS score at 90 days will be assessed using standardized forms and procedures in a telephone interview by certified research personnel blinded to the treatment allocation. To ensure blinding, certified research personnel will not have access to the patient's medical records, and they will instruct patients and their family members before interviews not to disclose the assigned treatment arm. The assessment of secondary clinical endpoints will not be blinded. Neuroimaging will be assessed by a core laboratory blinded for the clinical information.

Secondary efficacy and safety outcomes are listed in Table 3.

Data and safety monitoring board

The trial will be monitored by a data and safety monitoring board (DSMB) including neurologists, a neuro-interventionalist and an independent statistician. The role of the DSMB is to monitor the trial's safety and provide the steering committee with recommendations on the continuation or termination of the trial. DSMB will meet before the start of the study and twice a year thereafter during the patient recruitment phase. Safety assessments are required after every 5 symptomatic intracranial hemorrhages and after every 10 deaths, in accordance with the study protocol. The frequency of safety assessments may only be changed based on DSMB recommendations.

Sample size estimation

We calculated the sample size based on data from the Dutch MR CLEAN Registry[18] by comparing mRS distributions in the immediate CAS group (mRS 0: 17.9%, mRS 1: 22.3%, mRS 2: 16.7%, mRS 3: 14.4%, mRS 4: 12.3%,

Table 3. Efficacy and safety endpoints.

Primary efficacy endpoint
- mRS score at 90 days (ordinal distribution)
Secondary efficacy endpoints
- Excellent functional outcome (mRS 0–1) at 90 days
- Good functional outcome (mRS 0–2) at 90 days
- Independent ambulation (mRS 0–3) at 90 days
- NIHSS score at 24 h and day 5–7, or at discharge
- Adequate recanalization after EVT (mTICI 2b or higher)
- Final infarct volume on brain CT at 24 h
- Arterial occlusive lesion (AOL) score on CTA at 24 h
- Any ischemic stroke within 90 days
- Recurrent ipsilateral TIA/ischemic stroke within 90 days
- Carotid artery re-occlusion at 24 h and 90 days
- Quality of life (EQ5D-5L) questionnaire at 90 days
Safety endpoints
- Embolization in new vascular territories during EVT
- Incidence of bradycardia and/or hypotension during CAS
- Incidence of complications at the vascular access site (aneurysm, bleeding, vascular occlusion) within 72 h after EVT
- Incidence of symptomatic intracranial hemorrhage (sICH) defined as an increase in the NIHSS score of ⩾4 points or an increase in the score for an NIHSS subcategory of ⩾2 points with presence of parenchymal hemorrhage type 2 according to the Heidelberg criteria[17] within 90 days
- Any intracranial hemorrhage on brain CT at 24 h, classified according to the Heidelberg criteria.[17]
- Any extracranial hemorrhage within 90 days
- Any serious adverse event within 90 days
- Mortality at 90 days

mRS: modified Ranking Scale; NIHSS: National Institutes of Health Stroke Scale; mTICI scale: modified treatment in cerebral infarction scale.

mRS 5: 5.0%, mRS 6: 11.4%) and in the deferred treatment group (mRS 0: 6.9%, mRS 1: 20.2%, mRS 2: 17.9%, mRS 3: 16.4%, mRS 4: 17.2%, mRS 5: 8.0%, mRS 6: 13.4%). We calculated the assumed effect size to be a common odds ratio (cOR) of 1.15 for a shift in favorable direction across the full distribution of the mRS. The non-inferiority margin was set to a cOR of 0.8, corresponding to an absolute difference of approximately 5% in favorable outcome (defined as mRS 0–2). With an expected cross-over rate of 3% in each arm, a dropout rate of 2% and a 15% reduction in sample size after covariate adjustment, we estimated that a sample size of 600 patients (300 per group) would provide a power of 80% (at a two-sided alpha level of 0.05) to determine that the lower bound of the cOR 95% confidence interval (CI) does not exceed the non-inferiority margin of 0.8.

Statistical analysis plan

Baseline data will be reported by treatment allocation as categorical or continuous variables, where appropriate.

The main analysis of the trail consists of a comparison of the primary outcome at 90 days between the trial treatment groups. Statistical analyses will be performed according to the per-protocol (PP) principle as well as the intention to treat (ITT) principle. Both PP and ITT analyses must demonstrate non-inferiority to conclude that immediate CAS during EVT is non-inferior to a deferred treatment strategy.

The analysis of the primary efficacy endpoint will be fitted using an ordinal logistic regression model adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. The primary effect parameter will be expressed as the adjusted common odds ratio (acOR) for a shift in a favorable direction on the full mRS across the treatment groups (immediate CAS vs deferred treatment) with a two-sided 95% confidence interval (CI). When the lower limit of the 95% CI for acOR falls above the non-inferiority margin of 0.8, immediate CAS will be considered non-inferior to a deferred strategy. If non-inferiority is shown, a test for superiority will be applied.

An interim analysis on efficacy will be performed after 300 included patients have reached their 90-day follow-up. For the interim efficacy analysis, the DSMB will analyze the distribution of mRS scores at 90 days in both arms. The Haybittle-Peto boundary rule for premature termination of the trial will be applied, with a p-value threshold of less than 0.001.[19] Only the decision to continue or stop the trial for efficacy reasons will be communicated to the steering committee.

Secondary efficacy parameters will be assessed with linear, logistic or ordinal regression, where appropriate, adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA, and onset to randomization time.

A detailed statistical analysis plan is available in the Supplemental Data and, a separate, detailed analysis plan will be provided for the quality of life and cost-effectiveness analysis.

The results of the trial will be reported following the Consolidated Standards of Reporting Trials (CONSORT) statement and its extension about non-inferiority studies[20]

Discussion

The primary objective of the CASES trial is to assess the efficacy of immediate CAS during EVT among patients with acute ischemic stroke due to a carotid tandem lesion of presumed atherosclerotic origin and compare this with the strategy of deferred treatment (including best medical treatment only) of the proximal ICA stenosis according to the guidelines. Second, this trial will compare the safety of these two strategies regarding the incidence of symptomatic intracranial hemorrhage, mortality, recurrent stroke and early proximal ICA re-occlusion. Third, the CASES

trial will compare quality of life and cost-effectiveness of both strategies.

At present, the most effective and safe approach to treat the proximal ICA lesion during EVT in patients with acute ischemic stroke due to a tandem lesion is still uncertain. Immediate CAS could improve cerebral perfusion and prevent recurrent stroke. Additionally, patients would not need a second invasive treatment for secondary prevention. However, a direct stenting approach may also carry some disadvantages. A major concern in acute CAS is the direct need for (double) antiplatelet therapy to prevent in-stent thrombosis, which may lead to an increased risk of hemorrhagic complications. This risk might be particularly pronounced in patients who have received intravenous thrombolysis prior to EVT or who present with a large baseline core infarct volume. Some patients may not show improvement after EVT, resulting in severe disability. Under these circumstances, physicians routinely opt against carotid revascularization by CEA or CAS during the follow-up phase, choosing instead to pursue only best medical management. Therefore, the benefit of early CAS in patients randomized to the immediate CAS arm might be questionable in hindsight.

Despite these concerns, several patient registries have found that EVT combined with immediate CAS results in better functional outcomes and a greater likelihood of successful reperfusion.[1,8,9] Furthermore, systematic reviews and meta-analyses have shown that CAS during EVT is associated with successful reperfusion and a better 90-day functional outcome, with no difference in mortality compared to EVT alone (with or without balloon angioplasty).[10–12] The EASI trial could only demonstrate the feasibility of randomizing patients with tandem lesions, but with only 24 patients included, no high-quality randomized data on efficacy or safety are available to date.[21]

Currently, there are four other ongoing prospective, randomized trials addressing the issue of safety and efficacy of immediate CAS during EVT in patients with acute ischemic stroke due to a tandem lesion: the EASI-TOC trial (*NCT04261478)* in Canada, The Thrombectomy in Tandem lesion (TITAN) trial (NCT03978988)[22] in France, the Proximal Internal Carotid Artery Acute Stroke Secondary to Tandem or Local Occlusion Thrombectomy Trial (PICASSO) trial (*NCT05611242)* in the United States of America and the Stent Implantation Versus Balloon Dilatation for Acute Anterior Circulation Tandem Occlusion (START) trial (*NCT05902000*) in China. Several differences in trial design exist compared to the CASES study. First, unlike the CASES study, the other four trials do not employ a non-inferiority design. This design is based on the assumption that immediate CAS is likely to be more cost-effective and less invasive, as it may prevent additional hospitalization costs and revascularization surgery in patients who would otherwise be scheduled for CEA. We involved patients in the design process, and their preference for a single procedure – provided it did not affect outcome – guided our choice for a non-inferiority approach. Additionally, while the other studies focus on patients with ipsilateral high-grade stenosis of the proximal ICA (greater than 70% or even near and complete occlusion), we selected a 50% stenosis threshold. This reflects the eligibility for deferred carotid revascularization treatment starting at 50%, while also considering the importance of cost-effectiveness in a non-inferiority trial. Similar to the CASES trial, the other trials leave the approach to treatment of the extracranial lesion in the comparator arm to the discretion of the treating interventionalist. Third, the primary endpoint in the TITAN trial is a composite measure, including reperfusion and neurological improvement (mTICI 3 and an improvement in NIHSS of at least 4 points between admission and day 1), whereas the PICASSO, EASI-TOC and CASES trials focus on functional outcome. Functional outcome measures are widely accepted in stroke research and facilitate comparison of the study intervention with other new strategies or indications within EVT. Finally, the TITAN trial also includes other causes of carotid artery lesions beyond atherosclerotic etiology, such as carotid artery dissections. However, due to pathophysiological differences and the low prevalence of these rather rare etiologies, the results may not support definitive recommendations for these subgroups. Consequently, we opted for a more homogenous population with tandem lesions of atherosclerotic origin to enhance robustness of the CASES trial findings.

The CASES trial design is pragmatic. We chose to leave certain decisions such as stenting device or stenting approach (anterograde vs retrograde stenting) at the discretion of the treating physician, to show results that are generalizable and representative of clinical practice. Similarly, by allowing the inclusion of patients based on the investigator's judgment of EVT eligibility (for instance, patients with a mild NIHSS but disabling symptoms), we aimed to reflect real-world scenarios where thrombectomy may still be considered. If the immediate CAS approach is non-inferior to the deferred treatment strategy, it is very likely that immediate CAS will become standard practice. This change could benefit both individual patients and the health care system, as it may prove to be more cost-effective, less-invasive and more patient-friendly. The current trial design allows for the evaluation of the efficacy and safety of immediate CAS in patients undergoing EVT for acute ischemic stroke due to a tandem lesion; in addition, a separate study assessing the long-term outcome of immediate CAS will be performed within the CONTRAST collaboration.

The CASES trial includes patients using a deferred written informed consent procedure. This approach is justified as immediate EVT is crucial to improve functional outcome.[23] Delaying EVT to obtain consent beforehand has been shown to reduce the patient's chances of recovery.[24]

Additionally, patients suffering an acute ischemic stroke often cannot make informed decisions themselves due to neurological deficits, and seeking consent from a proxy again causes delay.[25] Therefore, the use of a deferred consent procedure will result in better generalizability of the trial results by reducing the risk of selection bias. This approach has been successfully used in recent acute ischemic stroke trials conducted within the CONTRAST consortium.[26]

CASES is currently ongoing in 27 sites in Belgium and the Netherlands. As of December 19, 2024, 356 patients have been randomized, with recruitment of the remaining patients and follow-up scheduled for completion by July 2026.

Summary and conclusions

CASES is a phase-3 multicenter randomized clinical trial with a PROBE design. By evaluating the efficacy and safety of immediate CAS during EVT of acute ischemic stroke patients with tandem lesions, we hope to demonstrate non-inferiority of the immediate CAS approach, which would impact current guidelines regarding treatment recommendations in these patients.

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Declaration of conflicting interests

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Ethical approval

In place at all recruiting sites.

Informed consent

The medical ethical committee approved the use of deferred consent, recognizing that the CASES trial involves the investigation of an acute intervention in an emergency setting for a life-threatening disorder. The investigators will obtain written consent from all patients or their representative after the endovascular procedure.

Trial registration

ClinicalTrials.gov NCT06511089; ISRCTN 14956654

Guarantor

MU

Contributorship

All authors were contributors to protocol development, gaining ethical approval, patient recruitment, study procedures, and data management. LM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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