Evaluation of direct transfer to angiography suite vs. computed tomography suite in endovascular treatment. Randomized clinical trial

Study code: ANGIOCAT

Abstract

Rationale: Transferring patients directly to the angio-suite (DTAS) after admission leads to significant reduction of in-hospital times and has shown safety and efficacy in selected patients in three retrospective studies.

Aim: To explore the safety and benefit of DTAS in patients with suspected large vessel occlusion (Rapid Arterial oCclusion Evaluation (RACE) scale >4) within 6 hours from symptoms onset by reducing workflow times as compared to a traditional CT admission protocol.

Design: Randomized, prospective, open clinical trial with a primary outcome evaluated by a blind investigator.

Procedure: Eligible patients must be 18 of age or older. A large vessel occlusion must be suspected based on a prehospital rapid arterial occlusion evaluation >4 within 6 hours from stroke onset. The admitting CSC must be pre-notified by emergency medical services and the angio-suite and the treating team must be available. Patients will be randomly allocated to DTAS versus traditional neuroimaging following a 1:1 ratio.

Study outcome: The primary endpoint is the modified Rankin Scale score at 90 days. The primary safety outcome is mortality at 90 days.

Trial registry name: Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial (ANGIOCAT).

Trial URL: https://clinicaltrials.gov/ct2/show/NCT04001738

Trial registration number: NCT04001738

Background

The safety and efficacy of endovascular treatment (EVT) in acute stroke have been demonstrated in several trials(1). The relevance of time from onset to reperfusion was confirmed in these trials: for each 9 minutes delay in achieving reperfusion, one in every one hundred of patients undergoing EVT will present a worse outcome measured by modified Rankin scale (mRS)(2). Other studies determined that for each 30 minutes delay, the chances of achieving a 3-months favorable outcome decreased 10-15%(3). For this reason, strategies to improve prehospital and in-hospital workflows are being developed.

On one hand, strategies focused on identifying patients with a high suspicion of LVO and determine to which hospital the patients should be transferred. Many studies have demonstrated the usefulness of prehospital scales with the aim of reducing delays(4). The RACE scale is a tool designed for paramedics and emergency medical services (EMS); it is a simplified NIHSS scale version that scores neurological deficits from 0 to 9(5). A score higher than 4 predicts the presence of large vessel occlusion (LVO) with a high sensitivity (85%) and specificity (68%). In Catalunya the RACE scale has been progressively implemented since 2014, and is currently reported in more than 95% of acute stroke codes before arrival to the admitting center.

Regarding, in-hospital workflow one of the most used indicators is time from arrival to groin-puncture. During this interval the stroke team has to evaluate the patient, confirm EVT indication and coordinate logistics that allows initiation of EVT. Usually the indication of treatment is supported by imaging (CT or MRI) which rules-out intracerebral hemorrhage or a large infarct core (ASPECTS<5) and confirms LVO. Neuroimage can be complemented by multiparametric CT or MRI even though guidelines recommend not basing the decisions on it within 6 hours form onset(6). Thanks to the team efforts several stroke centers have progressively reduced door to groin puncture times.

A recently published study among all acute stroke codes admitted to a CSC within 6 hours from the onset showed that in over 90% of patients did not have a large infarct core which contraindicated EVT (ASPECTS<6)(7). These data along with the conclusion from HERMES meta-analysis which suggests that EVT in ASPECTS<6 does not increase the complication rate and could be beneficial(1) led to consider the possibility of simplifying the selection protocol to reduce workflow times.

Following the coronary angioplasty protocols in acute myocardial infarction, some groups have investigated the safety and efficacy of DTAS circuits confirming the reduction of door to groin time up to 17 minutes without any safety concerns(8-10).

We recently published a case-control study (DTAS vs conventional neuroimaging) in which subjects were matched by time from onset to hospital arrival, age, NIHSS and occlusion location. The study concluded that 80% of patients who met the inclusion criteria presented a LVO and DTAS transfer to reduced time from arrival to groin-puncture to 16 minutes as compared to 70 minutes in the control patients. This study showed that DTAS increased the odds of achieving a favorable outcome at 3 months.

The aim of Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial (ANGIOCAT) is to explore the long term outcome following a DTAS protocol compared with conventional neuroimaging protocol.

Study design

ANGIOCAT is a randomized, prospective, open-label clinical trial with blinded assessment of the primary endpoint by an independent investigator.

Patients with suspected acute LVO identified by EMS are included. After confirmation of inclusion and exclusion criteria by the stroke neurologist at patient arrival, patients are randomized to one of two study rms:

1. Direct transfer to Angiography Suite (DTAS) where the EVT team is waiting for the patient. A FP-CT is performed to discard intracranial hemorrhage (ICH) or large established ischemic lesions which would contraindicate endovascular treatment. Afterwards a diagnostic angiogram is performed to confirm the presence of a LVO. If indicated, intravenous-tissue Plasminogen Activator (iv-tPA) can be initiated immediately after cone beam CT.
2. Direct transfer to CT (DTCT) suite where the usual neuroimaging protocol is performed including NCCT, CT angiography and CT perfusion. Within 6 hours from symptom onset CT perfusion could be requested by the treating physician. Once the imaging results are analyzed the treating team will indicate the reperfusion treatments according to current guidelines.

Independently of the allocated protocol, all patients receive equal care during admission in the stroke unit or ICU. Thrombectomy might be performed with any EMA approved thrombectomy device, at the discretion of the interventionalist. For patients with stenosis or occlusion of the cervical internal carotid artery due to atherosclerosis, carotid angioplasty with or without stenting is permitted as part of the acute intervention.

The study protocol was approved by the medical ethics committee (PR(AG)156/2018). All patients or their surrogates provided written informed consent.

Patient population

ANGIOCAT trial is a unicentric study however there was the possibility to incorporate new stroke centers with previous experience in DTAS protocols. Our center is a Comprehensive Stroke Center (CSC) with a high volume of cases (≈300 EVT per year) and more than 2 years of experience with DTAS protocol (>150 DTAS cases) when the study started. Among DTAS patients, two thirds are secondarily transferred from a primary stroke center.

Patients that met all eligibility criteria were considered for enrolment if angiography suite and EVT team were available. We included stroke codes with suspected LVO (defined as prenotified Rapid Arterial Occlusion Evaluation (RACE) score >4 from EMS or from a primary stroke center (PSC), and confirmed National Institutes of Health Stroke Scale (NIHSS) score >10 at arrival by stroke neurologist) within 6 hours of symptom onset and a premorbid functional score of 2 or less on the modified Rankin scale (mRS).

Patient eligibility criteria

Inclusion Criteria:

1. Acute code stroke with clinically suspected Large vessel occlusion (RACE>4) within 6 hours from stroke onset either:
    a. Activated by EMS with prenotification
    b. Transferred from a primary stroke center.
2. Confirmation of NIHSS>10 at arrival by vascular neurologist.
3. Age ≥18 years.
4. Premorbid functional independence (mRS≤2)
5. Immediate availability of angiography suite.
6. Immediate availability of Endovascular treatment team (Neurologist, Interventionist, anesthesiologist, Nursery, Technicians…).
7. Deferred informed consent obtained from patient or acceptable patient surrogate (after the acute phase) was approved by the ethics committee.

Exclusion Criteria:

1. Hemodynamically unstable patients with requirement of advanced vital support.
2. Patients with limited life expectancy (<6 months) due to terminal disease.
3. Participation in any other clinical trial with a drug or device which could influence the outcome.
4. Patients with neurological or psychiatric disease that could undermine future evaluations.
5. Lack of disponibility for 90 days tracing.

Randomization

Pre-alert to the stroke neurologist before randomization. To ensure a high sensitivity and specificity to identify directly admitted to CSC patients, EMS contacted the stroke neurologist on call by telephone upon identification of an acute stroke patient with a RACE score >4 and time from symptom onset <6 hours. Transferred patients

from a Primary Stroke Center were previously evaluated by a local neurologist or Telestroke and study criteria were checked. After arrival at CSC, stroke neurologist confirmed that the inclusion criteria were met and patients were enrolled the patient in the ANGIOCAT study.

Randomization and minimization. Patients were randomly allocated to DTAS or DTCT in a 1:1 ratio, following a randomization sequence provided by an independent investigator. To avoid an imbalance in the primary/secondary admission rate between the study groups a blocked randomization according to transfer provenance was performed: primary (no previous neuroimaging) versus transfer from other center (previous neuroimaging).

Intervention

Patients included in the study are assigned to one of two different protocols:

- DTCT: After a fast neurological evaluation, patient will be transferred to CT suite where the usual neuroimage protocol will be performed. After imaging evaluation patient will be transferred to angiography suite if is eligible to EVT (reference intervention)
- DTAS: After a fast neurological evaluation, patient will be direct transferred to angiography suite where EVT team will be waiting for it (experimental intervention).

Clinical and radiological assessment

All patients underwent clinical assessment including RACE on ambulance by EMS staff; NIHSS was assessed on admission, and during follow-up 24 hours, 5 days and at discharge, and mRS was evaluated at discharge by stroke neurologists. Relevant workflow times (symptoms onset, hospital admission, imaging acquisition, iv-tPA bolus, arterial puncture, reperfusion) were recorded by stroke neurologists. Functional outcome at 90 days was evaluated through a structured telephone-based interview performed by a central assessor blinded to group assignment. The missing data-handling method for the primary outcome endpoint (90 days mRS) will be: for patients in which vital status is known to be “alive”, last observation will be carried forward; for patients in which vital status is unknown imputation of worst value (mRS=6) will be provided.

Radiological variables as baseline Alberta Stroke Program Early Computed Tomography Score(11) (ASPECTS; range, 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan), baseline

presence and location of LVO (CTA or digital subtraction angiography), 24 hours follow-up CT or magnetic resonance imaging for the discard an intracranial hemorrhage were assessed by local neuroradiologists. Local interventional physicians assessed reperfusion status using the modified Thrombolysis in Cerebral Infarction (TICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion)(12).

Outcomes

Primary outcome.

The primary outcome is the mRS score at 90 days among ischemic stroke patients with confirmed LVO whether they received or not EVT (ITT population), as evaluated through a structured telephone-based interview performed by a central assessor who is blinded to group assignment. The primary analysis is the shift analysis of the mRS using an ordinal logistic regression to estimate the common OR.

Secondary efficacy outcome.

1. Time from door arrival to groin puncture (for patients receiving endovascular treatment).
2. Dramatic early favorable response as determined by an NIHHS <2 or NIHSS improvement ≥ 10 points at 24 hours in patients with LVO.
3. Rate of mRS ≤ 2 at 90 days among ischemic stroke patients with LVO.
4. Rate of patients receiving EVT
5. Analysis of the above objectives in different subgroups: primary vs secondary transferred patients, ≤3 vs >3 hours from onset, NIHSS ≤15 vs >15, age ≤80 vs >80 years old.

Safety outcomes

Safety outcomes will be evaluated in the entire study population:

1. Rate of neurological deterioration (≥4 NIHSS points increase) from baseline
2. Rate of patients with neurological complications, mainly symptomatic hemorrhagic transformation.
3. Procedural complications (new territory emboli, arterial perforation, arterial access complication, etc.).
4. Mortality at 90 days in all patients.

Data protection

Data collection (table 1) will follow a predefined protocol using an Excel datasheet template and moving afterwards to SPSS program for statistical analysis.. Data will be codified introduced following a numerical code to protect patient's personal data.

At the end of the study and once finished inclusion period, these data will be removed. This information will be guarded by the main investigator.

Sample size estimates

For sample size calculation preliminary results from our center and previous publications were used. We expect a 30 to 40 minutes reduction in door to groin puncture in the DTAS protocol. In patients with confirmed LVO undergoing EVT this could represent a 15% increase in the rate of mRS 0-2. The expected mRS 0-2 distribution would be DTAS (55%) versus CT (40%).

With this prediction, in order to achieve a statistical power of 75% to detect differences by a bilateral Chi-square test with a significance level of 5% and a 1/1 distribution per study arm the necessary sample size is 306 patients. In the last 12 months, 240 thrombectomies were performed in our center and over 100 patients have followed a DTAS protocol, thus we estimate an inclusion period of 3 years.

Patients will be followed for 90 days after treatment or up to death if it occurs first.

A first analysis will be performed after 150 patients are included and the study will finish if significant difference in functional outcome is demonstrated between both groups at 90 days.

We plan to perform one interim analyses, when the primary endpoint of 50% (150 patients with complete follow-up) is met. We assume a one-sided family wise error rate of 2.5%, a power of 75% and an OR of 1.70 (ln OR=0.5306) under the assumption of proportional odds. We will test against an OR of 1 (log OR=0) and we will use Pocock stopping boundaries for stopping the trial early due to superiority(13).. We will derive Z-values by dividing the estimated log OR from the ordinal logistic regression by its standard error. The Z-value follows a standard normal distribution and will be used to test the one-sided alternative hypothesis that the coefficient is higher than zero against the null hypothesis that the coefficient is lower than or equal to zero. The boundary for superiority of the active treatment over control at the interim analyses is Z statistics of 2.178 and alpha error of 0.029.

Statistical analyses

Primary outcome analysis will be performed in the modified intention-to-treat population (ischemic stroke codes with confirmed LVO). The primary analysis is a common odds ratio (OR) over the mRS at 90 days analyzed by ordinal logistic regression among ischemic stroke patients with LVO.

Secondary outcome analysis. Statistical significance for intergroup differences will be assessed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Student t or Mann-Whitney U test for continuous variables among patients with LVO in efficacy items and among all patients in safety end-points. A descriptive analysis of adverse events will be presented in aggregate and by event.

Multivariable logistic or ordinal regression analyses will be used to determine factors that could be considered as independent predictors of good functional outcomes. The analyses will be adjusted using the variables that present a trend ($p \leq 0.1$) or a statistical relationship with the explored outcome. The odds ratio (OR), along with its 95% CI based on logistic or ordinal regression, will be reported.

We will test heterogeneity of treatment effect by prespecified clinically relevant variables on the primary outcome using a multiplicative interaction term (treatment×prespecified variable) and mixed methods modeling.

Ethics and dissemination

ANGIOCAT study protocol was approved by the local ethics committee.

Any modifications of the protocol which may impact on the conduct of the study will require a formal amendment to the protocol approved by the ethics committee.

Conclusion

The ANGIOCAT study aims to provide evidence that for acute stroke patients with suspected LVO, a DTAS protocol (ultra-fast triage based on cone-bean CT in the angio-suite) can reduce workflow times and safely improve long term outcome as compared to a traditional neuroimaging selection protocol.

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Clinical data	Radiological variables
Demography data	Presence of intracranial hemorrhage
Medical story	Final infarct volume
RACE score determinate by EMS	ASPECTS score on baseline CT
NIHSS score at admission, after treatment, at 24 hours and at discharge	Presence of large vessel occlusion by CTA or angiogram
Etiology TOAST scale	LVO location
Workflow times: - Symptoms onset - Hospital arrival - Imaging - iv-tPA treatment - Groin puncture - Revascularization	**Endovascular treatment variables**
	Procedure duration
	mTICI score at the end of procedure
	First pass reperfusion
	Periprocedural complications
Length of admission	
Discharge destination	
Functional status measured by mRS at discharge and at 90 days (independent blind assessment).	

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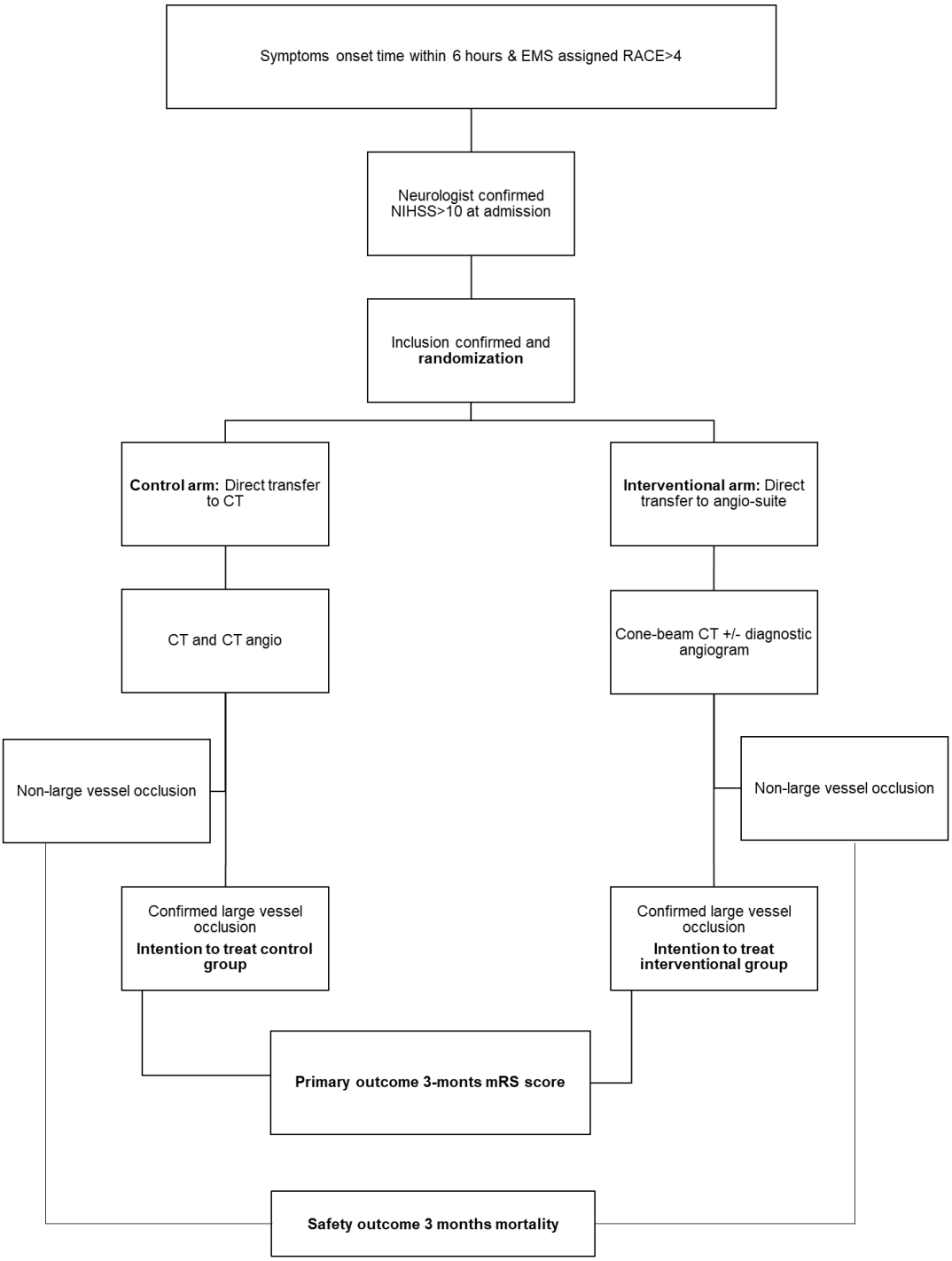
273 Table 1. Collected data. RACE: Rapid Arterial oCclusion Evaluation. EMS: Emergency
274 Medical Service. NIHSS: National Institutes of Health Stroke Scale. TOAST: Trial
275 Organization in Acute Stroke Treatment. ASPECTS: Alberta Stroke Program Early CT
276 Score. LVO: Large Vessel Occlusion. mTICI: modified Treatment In Cerebral Ischemia.



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278 Figure 1. ANGIOCAT study flow chart.

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