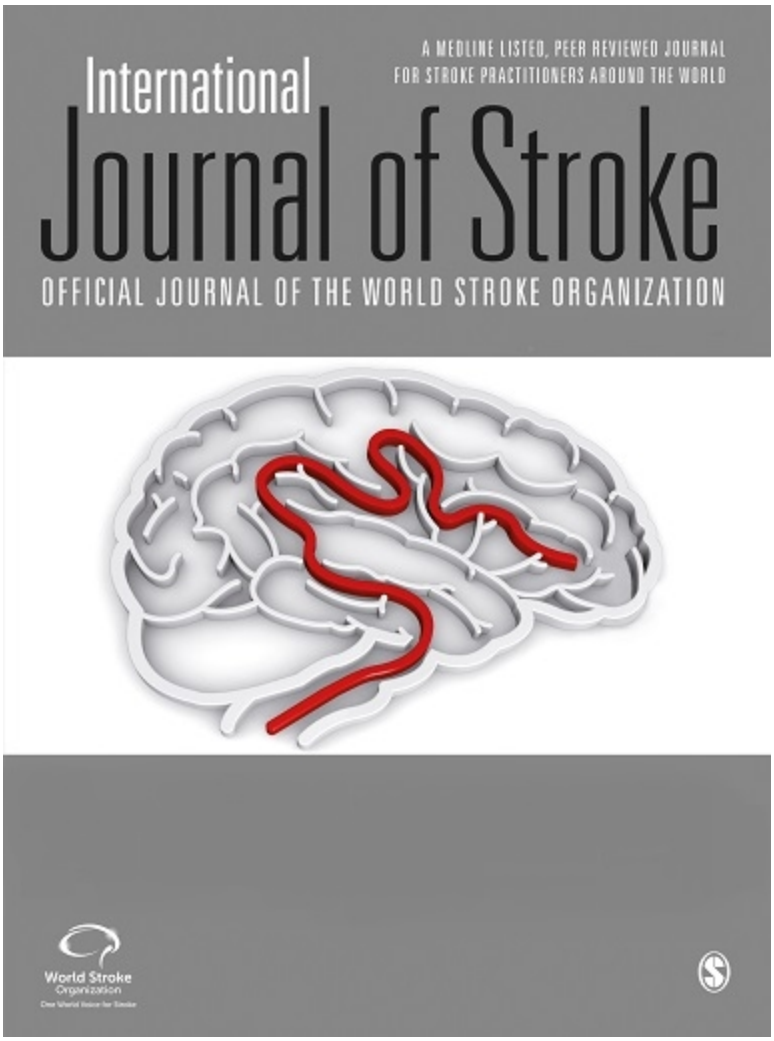

Transfer to the Local Stroke Center vs Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT): study protocol of a cluster randomized within a cohort trial

Journal:	*International Journal of Stroke*
Manuscript ID	IJS-12-18-6862.R1
Manuscript Type:	Protocol
Date Submitted by the Author:	21-Feb-2019
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Tables: 1
Figures: 4
Supplemental data: Statistical plan and Figure 1

Keywords: acute stroke, large vessel occlusion, pre-hospital, transfer models, drip and ship, mother ship, clinical trial.

ABSTRACT

Rationale: Optimal pre-hospital delivery pathways for acute stroke patients suspected to harbor a large vessel occlusion (LVO) have not been assessed in randomized trials.

Aim: To establish whether stroke subjects with RACE scale based suspicion of LVO evaluated by Emergency Medical Services in the field, have higher rates of favorable outcome when transferred directly to an Endovascular Center (EVT-SC), as compared to the standard transfer to the closest Local Stroke Center (Local-SC).

Design: Multicenter, superiority, cluster randomized within a cohort trial with blinded endpoint assessment.

Procedure: Eligible patients must be 18 or older, have acute stroke symptoms and not have an immediate life threatening condition requiring emergent medical intervention. They must be suspected to have intracranial LVO based on a pre-hospital RACE scale of ≥5, be located in geographical areas where the default health authority assigned referral stroke center is a non-thrombectomy capable hospital, and estimated arrival at a thrombectomy capable stroke hospital in less than 7 hours from time last seen well. Cluster randomization is performed according to a pre-established temporal sequence (temporal cluster design) with 3 strata: day/night, distance to the EVT-SC and week/week-end day.

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

Analysis: The primary endpoint based on the modified intention-to-treat population is the distribution of modified Rankin Scale scores (mRS) at 90 days analyzed under a sequential triangular design. The maximum sample size is 1754 patients, with two planned interim analyses when 701 (40%) and 1227 patients have completed follow-up. Hypothesized common odds ratio is 1.35.

INTRODUCTION AND RATIONALE

Despite the proven efficacy of intravenous (iv) thrombolysis in acute stroke patients, outcomes remain poor in those patients with occlusion of proximal large intracranial arteries[1]. The efficacy of iv thrombolysis in terms of arterial recanalization in the first hours progressively drops as the burden of the occlusive clot increases.[2] While the recanalization rate of an M2 occlusion is around 70%, the recanalization rates of M1 or terminal ICA occlusions drop to 30% and 10% respectively[3]. In patients with proximal LVO, the main advantage of iv thrombolysis treatment is that the treatment is readily available and can be promptly instituted even at centers lacking a sophisticated infrastructure.

On the other hand, endovascular treatment (EVT) has been shown to be a powerful treatment in patients with LVO stroke whether or not pre-treated wih iv t-PA, largely because effective reperfusion rates observed with this procedure are in the 80% range.[4] The counterpart is that, due to the nature of this treatment, a high level of technological resources and specialized physicians are needed, limiting the availability of this treatment to comprehensive stroke centers. This fact challenges the geographic equity in the access to EVT.

It seems clear that in the following years the number of trained interventionalists will grow and new EVT capable centers will appear. Still the presence of EVT capable centers in remote areas with low population density will not be justified.

At present we have 2 different strategies to manage stroke patients suspected to harbor a large vessel occlusion located in geographical areas not primarily covered by a EVT-SC. Transfer to the nearest primary stroke center where iv t-PA is administered with subsequent transfer to an endovascular center in case of LVO vs primary stroke center bypass and direct transfer to an endovascular center where both iv t-PA (if eligible) and endovascular treatment can be administered. While time to treatment initiation is of critical importance, in the first case iv t-PA is presumed to be administered faster but may not be effective in a large proportion of patients with proximal LVO, and a secondary transfer to an endovascular center implies a delay of time from onset to recanalization.[5] Conversely, adirect transfer to an endovascular center would result in faster initiation of thrombectomy at the presumed expense of delayed or even denied administration of iv t-PA. It is worth highlighting that only about 25-30% of patients selected with a RACE>4 are candidate to iv-tPA.[6] In both scenarios, time to treatment initiation is critical and the sooner the treatment is started, the higher are the chances of clinical recovery.[7] Currently, no randomized data are available to support the benefit of one approach versus the other.

In addition, several other issues should be considered. How safe is it to transfer these patients to more distant hospitals? Is there a distance beyond which there is no or very limited benefit from a direct transfer to an EVT-SC?

Theoretically the benefits of a primary transfer to an EVT-SC would only apply to patients with LVO and may unnecessarily delay treatment in all others. Therefore, the

predictive power of initial screening tools to identify patients with suspected LVO becomes of paramount importance. In our region we have developed the RACE scale which has been validated as a reliable tool for predicting the presence of LVO with approximately 50% predictive power including when used by paramedics region-wide.[8]

The overall goal of the RACECAT trial is to establish whether subjects with clinically suspected LVO at the pre-hospital level (established by a RACE scale score >4) and transferred directly to an EVT-SC, thus bypassing the local-SC, have a more favorable clinical outcome as compared with subjects transferred to the closest local stroke center. The RACECAT trial aims to provide answers to important logistic questions to streamline acute stroke systems of care and access to specific reperfusion treatments.

METHODS

Study design

RACECAT is a cluster randomized, mirroring real world care trial, with blinded-end-point assessment, that is embedded within a region-wide registry of acute stroke patients (CICAT) and focuses on patients with suspected acute large vessel occlusion (LVO) identified by Emergency Medical Services (EMS) at first assistance in the field. Two EMS routing strategies are compared: transfer to the closest local stroke center (Local-SC) vs. transfer to an endovascular stroke center (EVT-SC), according to a pre-established temporal sequence that remains concealed to the EMS technicians before the first patient within the cluster is transferred.

Option 1: Transfer to the nearest local-SC offers immediate care including rapid access to iv-thrombolysis. For LVO patients, subsequent transfer to an EVT-SC is organized, where the patient can arrive: recanalized (no further specific treatment needed), with a large infarct and no mismatch (no further specific treatment needed), or with persistent occlusion and mismatch (will receive EVT with time delay as compared with option 2). The time to admission to the EVT- SC will be determined by the initial distance to the Local-SC, the door-in/door-out (DIDO) time and the distance from Local SC to EVT-SC.

Option 2: Transfer to the nearest EVT-SC (bypassing the nearest local-SC) offers access to all effective treatments. The time to admission will only be determined by the distance to the EVT-SC. As compared to option 1, iv thrombolysis treatment is delayed (or even denied) but EVT initiation is advanced.

Patient population

The RACECAT study is being performed in the autonomous region of Catalonia, with the participation of Emergency Medical Services (EMS) and all the Stroke Centers: 6 Endovascular Stroke Centers (EVT-SC) and 19 Local Stroke Centers (Local-SC), 7 of them Primary Stroke Centers and 12 Telestroke Centers.[9]

The healthcare system of Catalonia integrates into a single network of public use

(SISCAT) all health resources to cover the entire population (7.5 million residents). As for acute stroke care, territorial planning occurred between 2006 and 2013 that eventually rolled out a network of Code Stroke hospitals dotted around Catalonia. The EMS, a public company within the SISCAT, is responsible for urgent prehospital care including Code Stroke patients as well as urgent interhospital transports. The Code Stroke Instruction of Catalonia set the activation criteria to be satisfied by the EMS upon acute stroke recognition, and all the Code Stroke-related EMS activity is included in the SITREM registry. In addition, the Code Stroke Instruction also established the need to continuously monitor the quality of the model based on mandatory inclusion of Code Stroke patients' data in a prospective registry (CICAT).

RACECAT eligible population includes patients located in geographical areas where the reference stroke center is a hospital not capable to offer EVT, covering a total population of 3.85 million inhabitants, with distance to an EVT-SC ranging from 20 to150 minutes, and an average transfer time between centers of 45 minutes.

Patient eligibility criteria

Inclusion criteria:

1. Stroke patients with suspected LVO identified by a RACE scale[9] score >4 evaluated by EMS professionals previous to the transfer to a stroke center: at the pre-hospital setting, in non-stroke ready centers or primary healthcare centers.

2. Patients located in geographical areas where the reference stroke center is a hospital not capable to offer EVT (Primary stroke Center or Telestroke Center).

3. Estimated arrival time to an EVT-SC <7 hours from symptom onset. Symptom onset is defined as the time in which the patient was last seen well.

4. No significant pre-stroke functional disability (modified Rankin scale 0 - 2)

5. Age ≥18

6. Deferred informed consent obtained from patient or acceptable patient surrogate (after the acute phase, as permission to use clinical data within a clinical registry was approved by the ethics committee)

Exclusion criteria

1. Patients in a coma (NIHSS item of consciousness >1).

2. Patients with unstable clinical status who require emergent life support care.

3. Serious, advanced, or terminal illness with anticipated life expectancy of less than 6 month.

4. Acute stroke patients with suspected LVO identified at the Emergency Department of a stroke center.

5. Subjects participating in a study involving an investigational drug or device if it is believed that participation in such a study would impact the results of this study.

6. Patients with a pre-existing neurological or psychiatric disease that would impair the neurological or functional evaluation.

7. Unlikely to be available for 90-day follow-up (e.g. no fixed home address, visitor from overseas).

Randomization

EMS pre-alert to the stroke neurologist before randomization

To ensure a high sensitivity to identify candidate patients, EMS contact the stroke neurologist on call by telephone upon identification of an acute stroke patient with the following conditions: RACE scale score >3 and time from symptom onset or last time seen well <8 hours. After EMS contact, the stroke neurologist confirms all the inclusion criteria and enrolls the patient in the RACECAT study.

Randomization

Consistent with the temporal cluster design of our study, transfer allocation to each of the two arms was carried out in a 1:1 ratio by 12-hour time-slots, following a randomized temporal schedule previously defined by an external statistician (Bioclever) and stratified by territory (metropolitan vs. provincial area) and week day (working vs. weekend day). This stratification was decided with the aim to ensure a balanced distribution between the two groups regarding the urban vs. rural location of the patient, the proportion of wake-up strokes, and the proportion of patients attended in non-working hours, which are factors that can influence access to EVT and clinical outcomes. The choice of randomization by 12-hour blocks of time, rather than by days or weeks, was set in order to ensure the least amount of blinding regarding transfer allocation.

Allocation

Assignment of the patient to one out of the two possible transfer options is performed in real time by a smartphone based automated system according to the predefined randomized time period schedule. During the EMS contact, the stroke neurologist enters basic data of the patient into the system and immediately receives the assigned intervention group and the study code number, that is communicated to the EMS coordination center so that the transfer can be consequently organized by the EMS.

A notification is automatically sent from the allocation software to the local investigator of the receiving center and to the data managers for every included patient. Moreover, the EMS coordinator center and the Stroke neurologist alert the physician in charge at

the allocated destination center (Local-SC or EVT-SC) of the upcoming urgent arrival of a newly included patient in the study.

Masking

Transfer group allocation cannot be blinded to EMS professionals or neurologists that attend the patient at the Stroke Center (Local-SC or EVT-SC). Although this might open the way to performance bias, all involved professionals are encouraged to treat the patients according to best clinical practice. Local investigators of the participating Stroke Centers, who are not blinded to the assigned group, will register secondary outcomes (risk of evaluation bias). However, in all patients, the primary outcome (modified Rankin Scale score at 90 days), is evaluated through a telephone call by a certified central assessor, blinded to group assignment.

Intervention

Patients included in the study are assigned to two different transfer models (Figure 1):

- Local-SC: Transfer to closest Local-SC as currently stated on the standard code stroke protocol (reference intervention).

- EVT-SC: Directly transferred to the EVT-SC bypassing the closest Local-SC (experimental intervention)

For patients allocated to the EVT-SC group with estimated transfers longer than 60 minutes, the following transport resources are prioritized as follow:

1. Helicopter Emergency Medical Services (with physician):

2. Advanced Life Support (with physician or nurse)

3. Basic Life Support (with emergency technicians) if an advanced ambulance is not immediately available.

Modification of allocated intervention

Modification or change of the allocated circuit is only allowed when neurological deterioration or severe medical complications during the transfer occur. In such case, the patient is transported to the nearest stroke center as soon as possible. All other deviations from initial destination due to other reasons will be analyzed as intention to treat but not in per protocol (see the Statistical Plan in the suplemental data).

Concomitant care and interventions prohibited during the trial

Other than initial decision about first transfer option patients receive standard clinical care according to each institutional protocols of each participating center, always in agreement with European Stroke Organization and national guidelines.

In local-SC, evaluation of EVT criteria and transfer to accredited EVT-SC when needed is mandatory for all patients. Contact with the EVT team from the local-SC is performed immediately after the neuroimaging confirming a LVO ischemic stroke or based on plain CT plus clinical criteria (NIHSS>=6 with cortical signs) in centers where vascular neuroimaging is not available, without waiting for response to iv-tPA if administered. ~~Patients included in the RACECAT trial will not receive EVT at any center not recognized as an EVT-SC by the local authorities.~~

Outcomes

Primary outcome

The primary outcome is the modified Rankin Scale score at 90 days in ischemic stroke patients 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 (with values 5, severe disability, and 6, death, collapsed) using an ordinal logistic regression to estimate the common OR.

Secondary efficacy outcomes

Pre-specified secondary analyses

1. To explore whether time to endovascular stroke center arrival, plays any role on the consistency of the intervention effect
2. To explore the consistency of the main effect on the (shift analysis) in the following populations: All patients / hemorrhagic / mimics
3. To explore the consistency of the main effect on the following subgroups:
    a. Age <80 // ≥ 80
    b. Gender male // female
    c. Eligible for iv t-PA // non iv t-PA eligible when attended by EMS
    d. Treatment with iv tPA // no treatment with iv tPA at the first hospital admission
    e. Confirmed prior mRS 0-2 // mRS >2 evaluated at hospital arrival
    f. Patients with values RACE scale 5-7 // RACE 8-9
4. Proportion of patients receiving iv tPA
5. Proportion of patients receiving EVT
6. Time from symptom onset to iv tPA administration (for patients treated with iv tPA) and to groin puncture (for patients treated with endovascular)
7. Dramatic early favorable response as determined by an NIHSS of 0-2 or NIHSS improvement ≥ 8 points at 24 (-2/+12 hours) hours in patients with ischemic stroke.

Secondary Safety outcomes

1. Mortality at 90 days in all patients.

2. Mortality at 90 days in intracerebral hemorrhage (ICH) patients.

3. Clinical deterioration requiring intubation during primary or secondary transfers.

4. Clinical deterioration (≥4 points on the NIHSS) at 24 hours.

Fig 2 shows the schedule of enrolment, interventions and assessments.

Data monitoring

Data collection

Trial data are part of the routinely collected data in ongoing stroke registries already implemented in Catalonia at the time of trial kickoff. For any given RACECAT patient, the data flow includes the following cohorts: SITREM, for prehospital EMS-related data; TICAT, for prehospital telestroke neurologist assessment of Code Stroke patients; and CICAT, for hospital-based data of Code Stroke patients (Figure 3).

The RACECAT electronic case report form is embedded in the CICAT registry since this dataset is linked to the SITREM and TICAT registries and captures specific information for the prehospital process of care. CICAT is a government-mandated, population-based registry of all Code Stroke activations reaching and being evaluated at any Stroke Center in Catalonia, where local investigators are responsible for registering any new case during admission. The CICAT registry has been adapted to include all data required for the RACECAT study (i.e. complications occurring during urgent EMS transfers, and the 5-day/ discharge visit). Since within our Code Stroke network, a given patient may be attended at different centers during the process of care, different investigators from different centers can fill in the different levels of the CICAT registry (Fig 1, supplementary data).

Every working day, a full-time dedicated general study coordinator (neurologist) checks all the patients included in the RACECAT study, confirms the signature of the informed consent by the patient or relatives, and contacts the participating centers to assure the compliance with the protocol and inclusion of clinical data in the registries.

Informed consent

Either patients or their legal representatives sign the informed consent form upon hospital arrival. Since inclusion of all Code Stroke cases in the CICAT registry is mandatory, the informed consent asks for permission to use all registry data within the framework of the trial, and for the telephone-based follow-up at 90 days. For cases in whom written consent cannot be obtained during hospital admission is not possible, the central coordinator makes efforts to obtain an oral, recorded consent through telephone call. For those other cases in whom written or oral consent cannot be obtained at any time, only a selection of unmonitored data included in the mandatory CICAT registry is

used for the study purposes. Patients without informed consent are not contacted at 90 days over the phone and the last mRS value (visit 5d) is carried forward. If informed consent is denied the patient's information will not be used in efficacy analyses, but vital status at 90 days will be included for safety analysis.

Data Auditing

All data entered in the CICAT registry are monitored by an external CRO (Anagram) through centralized monitoring performed at some of the participating centers where electronic health records for all Catalan citizens can be centrally accessed. Any data discrepancies are queried to the local investigator. Monitoring visits are performed to verify data accuracy and ensure queries are resolved.

Screening-log

RACECAT is designed as a population-based study. Monitoring of adherence to the study selection criteria is performed through monthly reviews of the EMS database (SITREM) to detect code stroke patients with RACE scale >4 not included in the study. Patients not included because EMS did not contact the stroke neurologist are registered as "potentially eligible but unscreened". Patients not included because the stroke neurologist detected any exclusion criteria are considered as "screening failures" and are registered in the TICAT database (Figure 3). Feed-back about the adherence to the study protocol is given to all investigators every month. Additional meetings take place in case of detecting inclusion problems in specific geographic areas.

Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board has been established. The purpose of the DSMB is to review, on a regular basis, accumulating data from the ongoing trial. The DSMB also evaluates the interim analyses, which are performed by an external statistician (Bioclever), according to the pre-written statistical analysis plan (Charter DSMB, Supplemental data). The DSMB is composed of three experienced stroke neurologists who are not participating in the study and are not affiliated with the sponsor. The DSMB could require the assistance of a statistician if considered necessary. The role of the DSMB is to: (1) make recommendations to the Study Executive Committee regarding stopping or extending the trial based on the pre-planned interim analysis; and (2) review the occurrence of adverse events and make recommendations to the Executive Committee regarding safety of the study. A strict control of predefined adverse events is ensured through monitoring by the CRO. The following SAEs are specially monitored: (1) Aspiration pneumonia within 5 days; (2) Clinical deterioration requiring intubation during EMS transfer to the stroke center assigned; (3) Clinical deterioration during the first 24h.

Sample size estimates

Effect size measure

According to data available from the RACE score validation study, we can assume that final diagnostic of patients with a RACE >4 for both groups of study are: 5% stroke mimics, 20% intracerebral hemorrhage (ICH), 25% acute ischemic stroke without LVO or re-canalized with iv-tPA (AIS-no LVO), 50% acute ischemic stroke with a persistent LVO (AIS-LVO). As ischemic patients constitute the target population, sample size calculation is based on the enrichment studies paradigm. As the expected ischemic and non-ischemic ratio is 3:1, recruited sample will be increased accordingly.

The proportion of ischemic stroke patients treated with EVT is estimated to be 30-35% in the EVT-SC group and 12% in the Local-SC based on the ex-ante rates in the areas directly covered by an EVT-SC and areas applying a drip-and-ship model. For the estimation of good outcome in each group, we considered the proportion of patients with good outcome (mRS≤2) for each particular diagnostic and treatment accordingly with previous scientific evidence: AIS-LVO treated with EVT (55%), AIS-LVO treated with EVT transferred from Local-SC (45%, expecting that onset to treatment in the Local-SC group will be probably 60 minutes longer, that corresponds to a 10% lower rate of good outcome according to a sub-analysis of REVASCAT trial), AIS-LVO not receiving EVT (30%) and AIS-no LVO (50%). Taking into account the expected distribution of diagnostics and treatments, the rate of good outcomes (mRS≤2) at 90 days for the intervention arm (direct to an EVT-SC) is estimated to be around 44%, and for the control arm (transferred to a Local-SC) is estimated to be 38% (Fig 4). These estimates yield an expected difference of 6% in the proportion of good outcome (mRS ≤2) (Figure 4).

Interim analyses rationale

We desired a maximum of 3 looks when approximately 40, 70 and 100% of the sample size complete the 90 days of follow-up, plus monitoring and data cleaning processes. A sequential test strategy was designed to have reasonable chances of stopping as soon as possible, either because of better efficacy of the intervention, because of the futility of the trial or because of safety reasons (Table 1).

At interim analysis, in case the stopping boundaries are crossed, the DSMB will recommend stopping the study either for efficacy, futility or safety (supplemental data). When addressing safety, DSMB will also consider mortality (mRS=6) and severe dependency (mRS=5) at three months as one single value. Once the interim analysis has been completed, the final decision to stop the study will be made by the steering committee at the recommendation of the data safety monitoring board. In case of early stopping, any overrunning patient will be followed until the end of the study and a final analysis will be performed.

Devised effect, power and sample size

The RACECAT trial is designed to test a shift common OR=1.348. We also analyze the trial properties under alternate more optimist (8%, 10%) and pessimistic (0%, 4%) scenarios. The ischemic population sample size required with these expected proportions and assuming one-sided Type I and Type II error probabilities of 0.025 and 0.20, respectively, is 1316. A triangular test with 2 interim looks (40/70% of sample recruitment) plus 1 final analysis is specified[11]. The number of patients and the theoretical probabilities to stop for efficacy or for futility at each interim look is showed in Table 1. Total sample size, including non-ischemic patients that will not compute for the final efficacy analysis is 1754.

An overall of 1316 ischemic patients (658 patients in each group) will provide a one-sided alpha risk of 2.5% if both compared treatments perform equally. The power will be 47.5% (80%, 95.5% and 99.4%) if the intervention improves by 4% (6%, 8% and 10%). Chances of stopping at each interim arm are also provided in table 1. For the 6% improvement, the theoretical probabilities of stopping at interim 1 (2 and 3) with a positive result of higher intervention efficacy are 32.8% (33.3% and 13.9%).

Statistical design

Primary end-point analysis

Main analysis is a common OR over the first 5 cut-points along the modified Rankin Scale (mRS) (shift analysis) at 90 days analyzed by Ordinal Logistic Regression. Therefore, the two worst mRS values (5 and 6) are treated as equal in the analyses.

Analysis of safety end-points

Mortality at 90 days will be assessed for all enrolled subjects and specifically for ICH patients. A Kaplan–Meier analysis will be generated and the mortality rates at 90 days between arms will be compared and 95% confidence intervals will be reported. Every attempt will be made to determine the status of each subject who withdraws from the study so that the withdrawal data can be used as a censoring point. A descriptive analysis of study-defined adverse events will be presented in aggregate and by event. Moreover, a descriptive analysis of other study-defined safety end-points will be presented, as clinical deterioration requiring tracheal intubation and clinical deterioration at 24h (NIHSS worsening ≥4 points or death at 24h).

A safety and administrative analysis will be performed after inclusion of the first 100 patients and thereafter every additional 300 enrolled patients. These analyses will be evaluated by the DSMB.

Ethics and dissemination

The RACECAT study protocol was approved by the local ethics committee of all

participating centers.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be approved by the corresponding Ethics Committees prior to implementation and notified to the health authorities in accordance with local regulations.

Conclusion

The RACECAT study aims to provide evidence that will help determine best practice in the prehospital workflow and management of suspected large vessel occlusion acute stroke patients.

Study organization and funding

Trial registry: ClinicalTrials.gov NCT02795962

Protocol V1. Issue date: Apr 23, 2016

Funding: The trial is sponsored by the nonprofit foundation *Fundació Privada Ictus Malaltia Vascular*, beneficiary of an unrestricted grant by Medtronic. Trial sponsor: *Fundació Privada Ictus Malaltia Vascular*. Elisabeth Ortínez (eortinez@fundacioictus.com)

Study sponsor and funders do not participate in the study design, collection, management, analysis and interpretation of data, writing of the report or the decision to submit results for publication.

Declaration of Conflicting Interests

Fees for consulting and talks

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS Group). Tissue plasminogen activator for acute ischemic stroke.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N. Engl. J. Med.* 1995;
2. Ribo M, Alvarez-Sabín J, Montaner J, Romero F, Delgado P, Rubiera M, et al. Temporal profile of recanalization after intravenous tissue plasminogen activator: Selecting patients for rescue reperfusion techniques. *Stroke*. 2006;37.
3. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007
4. Goyal M, Menon BK, Van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387.
5. Pérez De La Ossa N, Abilleira S, Dorado L, Urra X, Ribó M, Cardona P, et al. Access to Endovascular Treatment in Remote Areas: Analysis of the Reperfusion Treatment Registry of Catalonia. *Stroke* [Internet]. 2016;47:1381–1384. Available from: http://europepmc.org/abstract/med/27032445
6. Carrera D, Carrera D, Gorchs M, Querol M, Abilleira S, Ribó M, Millán M, Ramos A, Cardona P, Urra X, Rodríguez-Campello A, Prats-Sánchez L, Purroy F, Serena J, Cánovas D, Zaragoza-Brunet J, Krupinski JA, Ustrell X, Saura J, García S, Mora MÀ, Jiménez X, Dávalos A, Pérez de la Ossa N; Catalan Stroke Code and Reperfusion Consortium (Cat-SCR). Revalidation of the RACE scale after its regional implementation in Catalonia: a triage tool for large vessel occlusion. J Neurointerv Surg. 2018 Dec 22. doi: 10.1136/neurintsurg-2018-01451
7. Saver JL, Goyal M, Van Der Lugt A, Menon BK, Majoie CBLM, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: Ameta-analysis. *JAMA - J. Am. Med. Assoc.* 2016;
8. Pérez de La Ossa NP, Carrera D, Gorchs M, Querol M, Millán M, Gomis M, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion : The rapid arterial occlusion evaluation scale. *Stroke*. 2014;
9. Vivanco-Hidalgo RM, Abilleira S, Salvat-Plana M, Ribera A, Gallofré G, Gallofré M. Innovation in systems of care in acute phase of ischemic stroke. The experience of the Catalan stroke programme. *Front. Neurol.* 2018;9.
10. Todd S. A 25-year review of sequential methodology in clinical studies. Stat. Med. 2007

Roles and responsibilities – Committees

Principal investigator and research physician
Natalia Perez de la Ossa, Sònia Abilleira, Marc Ribo
Design and conduct of RACECAT
Preparation of protocol and revisions
Preparation of investigators brochure (IB) and CRFs [case report forms]
Organizing steering committee meetings
Managing CTO
Publication of study reports

Steering committee (SC)
Pere Cardona
Joaquín Serena
Francisco Purroy
Xabier Urra
David Cánovas
Dolores Cocho
Xavier Jiménez
Luis San Román
Antoni Dávalos (advisor)
Miquel Gallofré (advisor)
Carlos Molina (advisor)
Tudor Jovin (advisor)
Ángel Chamorro (advisor)
Erik Cobo (statistical advisor)
Agreement of final protocol
Reviewing progress of study and if necessary agreeing changes to the protocol

Trial management committee (TMC)
Antoni Dávalos (advisor)
Miquel Gallofré (advisor)
Carlos Molina (advisor)
Tudor Jovin (advisor)
Ángel Chamorro (advisor)
Erik Cobo (statistical advisor)
Study planning
Organization of steering committee meetings
Budget administration and contractual issues with individual centers

Data Managers
Rosa M. Vivanco-Hidalgo, Mercè Salvat-Plana, Guillem Gallofré, Anabel López, Montse Gorchs
Maintenance and data verification, informed consent management
Screening log

Mensual newsletters and feed-back

Table 1. Theoretical properties of the Triangular design for total N=1754 (N for ischemic=1316). Percentages indicates the probability of stopping at any interim, either for futility, for efficacy ('positive') or for any reason ('both'), considering the different values of the treatment effect Δ: the difference in the success rate. To facilitate reading, numbers are rounded and some percentages may not add up to 100%.

OLR (hypothetical)															
		H0: OR=1 (Δ=0)			H1: OR=1.225 (Δ=4%)			H1: OR=1.348 (Δ=6%)			H1: OR =1.478 (Δ=8%)			H1: OR =1.615 (Δ=10%)		
Total N	**N for ischemic**	**Futility**	**Positive**	**Both**	**Futility**	**Positive**	**Both**	**Futility**	**Positive**	**Both**	**Futility**	**Positive**	**Both**	**Futility**	**Positive**	**Both**
701	526	63,3%	0,9%	64,2%	16,4%	14,3%	30,7 %	5,5%	32,8%	38,3 %	1,4%	56,0%	57,4 %	0,3%	76,8%	77,0%
1227	920	29,2%	1,1%	30,2%	22,7%	20,5%	43,2 %	8,6%	33,3%	41,9 %	1,9%	32,4%	34,3 %	0,3%	20,7%	21,0%
1754	1316	5,0%	0,6%	5,6%	13,5%	12,7%	26,1 %	5,9%	13,9%	19,8 %	1,2%	7,1%	8,3%	0,1%	1,9%	2,0%
		97,5%	**2,5%**	100%	52,5%	**47,5%**	100%	20,0%	**80,0%**	100%	4,5%	**95,5%**	100%	0,6%	**99,4%**	100%
	Prob(Total N>701)	34,2%	1,6%	35,8%	36,1%	33,2%	69,3 %	14,5%	47,2%	61,7 %	3,1%	39,5%	42,6 %	0,4%	22,6%	23,0%

Figure 1. Intervention. Patients included in the study are assigned to two different transfer models: circuit A (drip and ship) and circuit B (mother ship).

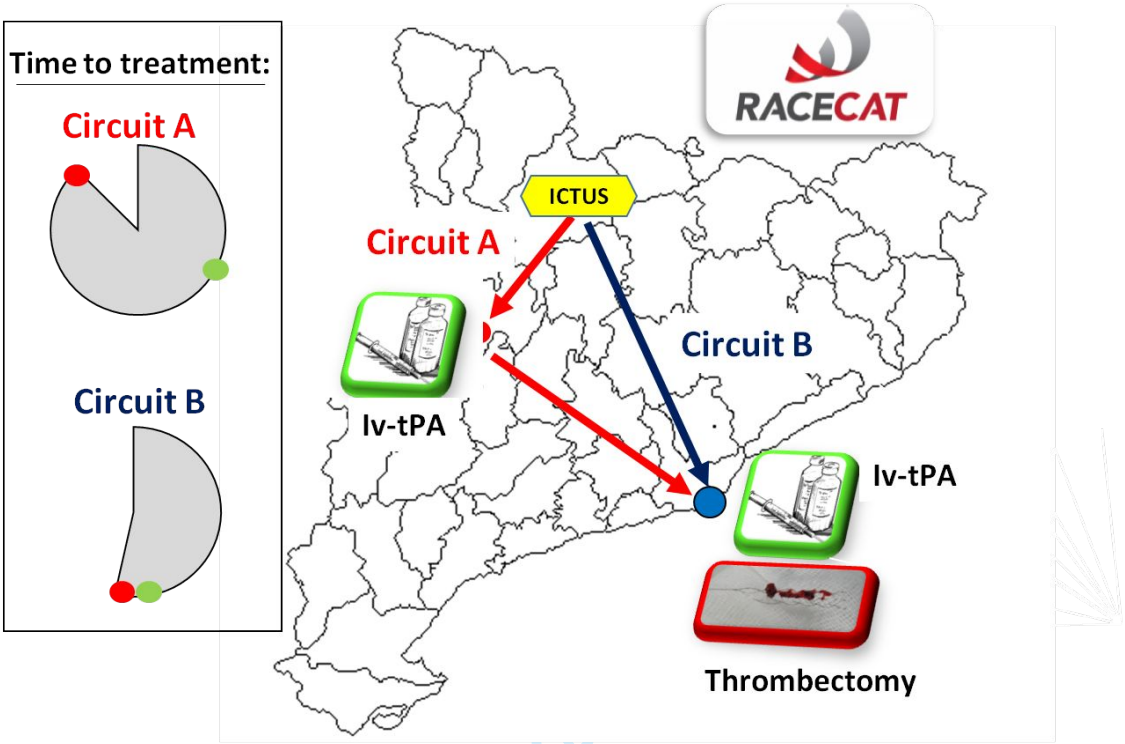


Figure 2: Template for the schedule of enrolment, interventions, and assessments.

	Enrolment	Allocation	Intervention	Follow-up (hospital admission)			Follow-up (90±15 days)
Time point	t-1	t0	t0	t1 (acute phase)	t2 (24h)	t3 (5 days or discharge)	t4
Enrolment:							
EMS identification	X						
Stroke Neurologist confirmation	X						
Eligibility criteria	X						
Allocation (randomization program by internet used by the Telestroke neurologist)		X					
Registry on the TICAT registry (Telestroke neurologist)		X					
Notification to the receptor center (Telestroke neurologist)		X					
Interventions:							
Direct transfer to **Ev-SC**			X				
Transfer to the **Local-SC**			X				
Secondary transfer from Local-SC to CSC (if candidate to EVT)				XX			
Return to the Local-SC					XX (if necessary)		
Assessments:							
Iv-tPA eligible when attended by EMS		X					
Clinical deterioration during transfer			X	X			
Prior mRS (at hospital)				X			
Medical history				X			
Stroke etiology				X			
Vital signs				X			
Baseline NIHSS				X			
Reperfusion therapy (iv-tPA or/and EVT)				X			
Time to reperfusion therapy				X			
NIHSS at 24h (-2/+12h)					X		
Severe adverse events				X	X	X	
mRS at 90 days[1]							X
Cost of care (parallel study)							X

[1]mRS to be done by an independent blinded evaluator through a structured telephone based interview.

Figure 3. Data collection

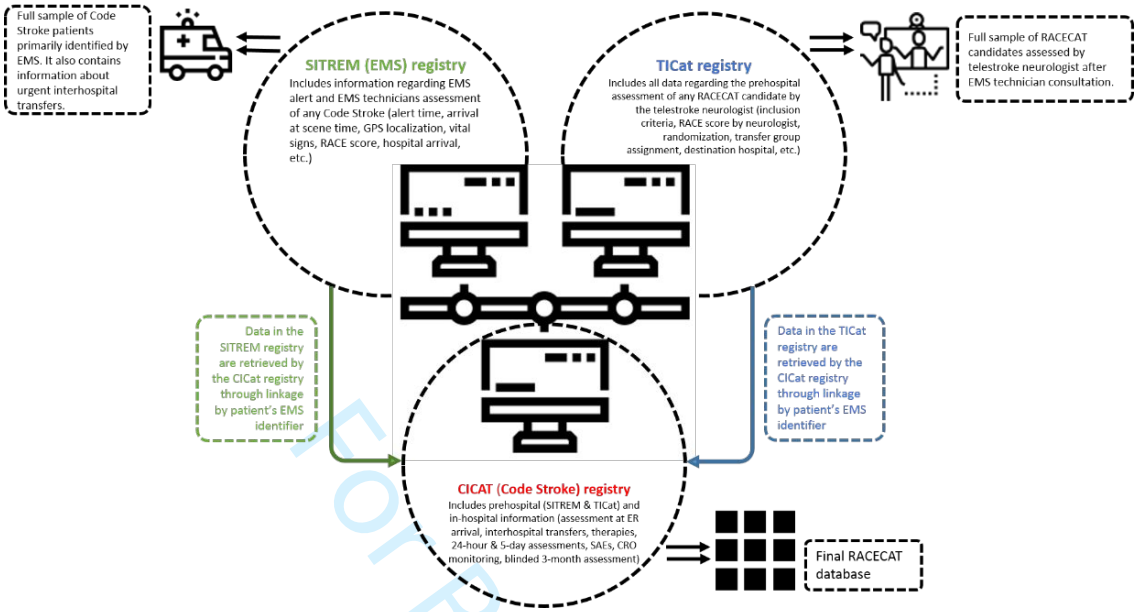


Figure 4. Estimated effect of the intervention, based on the diagnostic distribution and on the access to EVT in both groups.

Group: Local-SC

	AIS-no LVO	AIS-LVO No EVT	**AIS-LVO EVT**	
% of target pupulation (AIS)	33%	55%	12%	
% of good ouctome (mRS 0-2) for each group	50%	30%	45%[A]	
Good outcome estimation for Local-SC	16.5%	16.5%	5.5%	38.5%

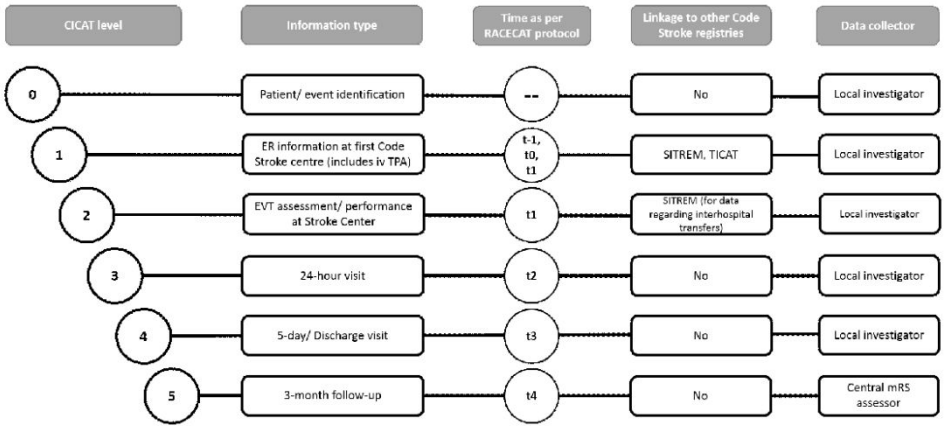
Group: EVT-SC

	AIS- no LVO	AIS-LVO No EVT	**AIS-LVO EVT**	
% of target pupulation (AIS)	33%	33%	33%	
% of good ouctome (mRS 0-2) for each group	50%	30%	55%[A]	
Good outcome estimation for Local-SC	16.5%	10%	18%	44.5%

[A] *Estimation of % of good outcome for AIS-LVO patients treated with LVO is 10% lower for Local-SC group considering the delay associated with inter-facility transfer (around 60min) (sub-study of REVASCAT trial).*

Supplemental

Figure 1. Organization of the CICAT registry



Supplemental material:
Informed consent form
SAP