REVASCAT: Update On A Recently Terminated Randomized Trial Of Mechanical Embolectomy With The Solitaire Device Versus Best Medical Therapy In Acute Stroke

(REVASCAT - clinicalTrials.gov, NCT01692379 )

A. Dávalos, and T. Jovin for the REVASCAT Steering Committee
Disclosures

- Study funded with an unrestricted grant by ev3-Covidien
- Sponsor: Fundació ICTUS (Non-profit foundation)
- Antoni Dávalos, MD: Consultancy fees (moderate) as member of the STAR steering committee
To evaluate the hypothesis that mechanical embolectomy with the Solitaire FR device is superior to medical management alone in achieving favorable outcome in the distribution of the modified Rankin Scale scores at 90 days in subjects presenting with acute large vessel ischemic stroke of less than 8 hours from symptom onset.
A Clinical Trial Within a Population Based Registry in Catalonia
Adequate infrastructure in Catalonia (7.5M inhab):
Stroke Program (Health Department), EMS stroke-code, hospitals network

Community hospitals (n= 11/35, with telemedicine)

Primary stroke centers (n= 9, excluding CSCs)

Comprehensive stroke centers (n= 5, 24h/7d)
SONIIA is a government-mandated, prospective registry aiming at CONTINUOUSLY MONITORING the QUALITY of ALL REPERFUSION THERAPIES administered to patients with acute ischemic stroke within the network of publicly financed acute hospitals in Catalonia.

SONIIA registry
Period Nov 24, 2012 to Dec 12, 2014

540 EVT patients
Overall population-based reperfusion treatment rates (per 100,000 inhabitants-year) in Catalonia

Population reperfusion treatment rates over time (2005 to 2014)

* 100,000 inhabitants-year

IV thrombolysis

all reperfusion treatments

ISC 2015 Nashville
REVASCAT Was Conducted in The Four Major Comprehensive Stroke Centers in Catalonia
Tertiary participating hospitals in REVASCAT (n=4)

• These centers perform 85% of reperfusion therapies in Catalonia and have neurointerventional teams available 24h
• Reperfusion therapies are consecutively and mandatory registered in SONIIA
• General consensus on equipoise
• Williness to randomize all eligible patients
• Uniform treatment modalities for treatment and control groups. Acute Stroke Units

• Potential advantages linked to a population based design
• Small homogeneous group of investigators & centers
• Potential exclusions from the target population were known and monitored
Study design

• Prospective, multicenter, randomized, controlled, sequential, open, blinded-endpoint trial.

• **Clinical sites:** 4 Comprehensive Stroke Centers available 24h/7 days in Catalonia

• The randomization employed a 1:1 ratio of Mechanical embolectomy with the CE MARK approved *stentriever Solitaire FR®* versus Medical management alone

• Randomization was done under a minimization process using:
  - Age (≤70 or >70 years)
  - Baseline NIHSS (6-16, or 17 or more)
  - Therapeutic window (≤4.5 or >4.5 hours)
  - Vessel occlusion site ( Intracranial ICA or M1)
  - Investigational center

Primary efficacy endpoint

• Distribution of the modified Rankin Scale scores at 90 days (shift analysis) as evaluated by two separate assessors who were blinded to treatment:

• Local certified neurologist

• Video recording of structured interview in the second half of the study adjudicated by a central rater (certified vascular neurologist)

Secondary efficacy endpoint

- **Infarct volume on CT at 24 hours** evaluated by independent Corelab
- **Vessel recanalization on CTA or MRA at 24 hours** adjudicated by a central independent Corelab
- **Dramatic favorable response** (NIHSS improvement ≥ 8 or NIHSS of 0-2 at 24 hours)
- **Primary endpoint evaluated at 1 year**
  - **Vessel recanalization (TICI 2b or 3)** on post procedure angiogram in the Solitaire arm adjudicated by a central Corelab.
- Quality of life analysis as measured by EuroQol/EQ5D at 3 months and 1 year
- Comparison of the primary and secondary outcome endpoints between trial patients and patients treated with endovascular reperfusion therapies outside the REVASCAT trial (**external validity**).

Safety endpoints (Adjudicated by an independent Clinical Events Committee)

- Mortality at 90 days from randomization
- Symptomatic intracranial hemorrhage (SICH) within the first 24 (-2/+12) hours confirmed by CT or MRI (SITS-MOST definition).
- Progressing stroke, malignant edema and hemicraniectomy
- Procedural related complications: groin hematoma, arterial perforation, arterial dissection, and embolization in a previously uninvolved vascular territory

Inclusion criteria

- Acute ischemic stroke ineligible for IV thrombolysis or where patient has received IV thrombolytic therapy **without recanalization after 30 min from tPA proven by CTA or MRA**
- No pre-stroke functional disability (mRS ≤ 1)
- Baseline NIHSS ≥ 6 points
- Age ≥18 and ≤ 80*
- Intracranial internal carotid (distal ICA or T occlusions) proximal MCA (M1) occlusion or tandem occlusions (proximal ICA + M1) **as evidenced by CTA, MRA, or angiogram.**
- Patient treatable (groin puncture) **within 8 hours** of symptom onset
- Informed consent

* Age was amended up to 85 year in mid 2014 when ASPECTS 9 or 10

Neuroimaging exclusion criteria

- Large early ischemic changes: Brain CT ASPECTS <7 or MR DWI ASPECTS <6.
- CT or MR evidence of hemorrhage (microbleeds were allowed in MR).
- Significant mass effect with midline shift.
- Evidence of carotid occlusion, high grade stenosis or arterial dissection *that could not be treated or* would prevent access to the intracranial clot.
- Occlusions in multiple vascular territories.
- Evidence of intracranial tumor (except small meningioma).

Statistical design

• Maximum simple size 690 patients (effect size 10%, OR=1.615)

• Achieving a common Odds Ratio ≥ 1.615 for improvement over first five cut-points along the modified Rankin Scale merging categories 5 and 6 (reduced shift analysis) at 90 days analyzed by Ordinal Logistic Regression accounting for the sequential design and considering minimization factors.”

• Triangular model with 3 interim looks: 174, 346 and 518 patients completed

Representation of the sequential design showing the position of the stopping limits.

# Schedule of key interventions and assessments

<table>
<thead>
<tr>
<th>Time point</th>
<th>Enrolment</th>
<th>&lt; 8 h</th>
<th>24 ± 12 h</th>
<th>5 ± 2 days or discharge</th>
<th>90 ± 14 days</th>
<th>1 year</th>
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</thead>
<tbody>
<tr>
<td><strong>Enrolment</strong></td>
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<tr>
<td>Baseline details</td>
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<tr>
<td>Eligibility screen</td>
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<tr>
<td>Informed consent</td>
<td>X</td>
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<tr>
<td>Allocation (Trial website)</td>
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<tr>
<td><strong>Interventions</strong></td>
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<tr>
<td>Best medical treatment</td>
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<tr>
<td>Angiogram¹</td>
<td></td>
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<td>X</td>
<td>X</td>
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<td>Thrombectomy¹</td>
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<tr>
<td>ASU or ICU admission</td>
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<td></td>
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<tr>
<td><strong>Assessments</strong></td>
<td></td>
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<td></td>
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<td>Modified Rankin Scale score</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT-CTA or DWI-MRA (CTP/PWI if &gt;4.5h)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Thrombus location &amp; TICI</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

1. Solitaire treatment arm

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Onset of the stroke (last time the subject was last known well)
Baseline Imaging study assessing vessel patency
Time of randomization \( \text{t}=0 \)
Medical management alone Vs Endovascular procedure
In-Hospital Post Treatment Assessment
Follow-up Assessment at 90 (± 14) Days
Follow-up Assessment at 6 and 12 months (±14 days)


ISC 2015 Nashville
Procedure requirements

• Angioplasty or stenting of intracranial vessels not be allowed (may be used for extracranial ICA stenosis/occlusion).

• Only Solitaire FR allowed: Neither rescue pharmacological thrombolysis nor mechanical thrombectomy

• Interventional neuroradiologists or interventional neurologists: > 3 years expertise, > 20 thrombectomies with Solitaire FR

• Balloon guide catheter strongly recommended

• No more than 6 passes per vessel (3 passes per device)

• Sedation or intubation is discretionel

• Angiographic images after deployment and retrieval for each pass and the time of each deployment must be recorded.
Trial cumulative enrollment

Recruitment rate 2.2 patients/center/month

- Estimated
- Randomized

In December 12th, 2014, the DSMB recommended discontinuation after the preplanned 1st interim analysis (n=206)

1st projected sample of sequential analysis (n=174)

All (4) centers active

2nd projected sequential analysis (n=346): Oct-2015
3rd projected sequential analysis (n=508): Jan-2017
Last projected interim analysis (n=690): Jun-2018
Baseline characteristics at the first interim sample (n=174)

<table>
<thead>
<tr>
<th>Work-flow in min. (median, 95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Onset to hospital arrival</td>
</tr>
<tr>
<td>Onset to groin</td>
</tr>
<tr>
<td>Imaging to groin</td>
</tr>
<tr>
<td>Random to groin</td>
</tr>
</tbody>
</table>

| Mean age (SD)                     | 65.9 (10.4) |
| Median NIHSS                      | 17 (13-20)  |
| IV tPA                            | 127 (73%)   |

### Table 11 Minimization factors

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Total no-missing</td>
<td>n</td>
</tr>
<tr>
<td>&lt;= 70 years</td>
<td>n (%)</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>n (%)</td>
</tr>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Baseline NIHSS</th>
<th>Total</th>
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<tbody>
<tr>
<td>Total no-missing</td>
<td>n</td>
</tr>
<tr>
<td>17 or more</td>
<td>n (%)</td>
</tr>
<tr>
<td>6 - 16</td>
<td>n (%)</td>
</tr>
<tr>
<td>Missing</td>
<td>n</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occlusion site</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no-missing</td>
<td>n</td>
</tr>
<tr>
<td>Intracranial internal carotid artery (ICA)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Proximal middle cerebral artery (M1 segment)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Tandem occlusions (proximal ICA plus terminal ICA or M1 segment)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Missing</td>
<td>n</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Therapeutic window</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no-missing</td>
<td>n</td>
</tr>
<tr>
<td>&lt;= 4.5 hours</td>
<td>n (%)</td>
</tr>
<tr>
<td>&gt; 4.5 hours</td>
<td>n (%)</td>
</tr>
<tr>
<td>Missing</td>
<td>n</td>
</tr>
</tbody>
</table>
SONIIA monitoring of consecutive enrollment into the trial

Stroke patients with endovascular treatments performed within 24/Nov/2012 and 12/Dec/2014 at any of the 6 hospitals with capacity to perform endovascular treatments in Catalunya

76 Endovascular treatments performed in non REVASCAT hospitals

30 REVASCAT eligible patients identified in the 2 non REVASCAT hospitals

68 eligible patients treated outside the trial

8 true REVASCAT eligible

8/214 = 3.7%

464 Endovascular treatments performed in REVASCAT hospitals

170 REVASCAT eligible patients identified in the 4 REVASCAT hospitals

102 patients randomized to the REVASCAT-IA

60 exclusion criteria undetected by the registry

Patients randomized to the REVASCAT-BMT

206
Trial stopping rules and definitive enrollment suspension

On December 12, 2014, following the first pre-planned interim analysis of 174 patients, the DSMB concluded that equipoise did not longer exist in REVASCAT population and recommended discontinuation of the study. Accordingly, the Steering Committee closed enrollment permanently in REVASCAT. Completed evaluation of the 206 patients finally enrolled is estimated for mid March. Main primary and secondary outcomes will be presented in the European Stroke Organization (ESO) Conference in Glasgow, April 17th, 2015.
Executive Committee

Co-Principal Investigators:
Antoni Dávalos (Barcelona)
Tudor G Jovin (Pittsburgh)

Members:
Angel Chamorro (Barcelona)
Erik Cobo (Barcelona)*
Maria A. De Miquel (Barcelona)
Carlos Molina (Barcelona)
Alex Rovira (Barcelona)
Luis San Román (Barcelona)
Joaquín Serena (Barcelona)

DSMB

Gregory Albers (Stanford)
Kennedy Lees (Glasgow)
Juan Arenillas (Valladolid)
Robin Boberts (Hamilton)*

Clinical Events Committee

Brian Jankovitz (Pittsburgh)
Joan Martí-Fàbregas (Barcelona)

Centers & Principal Investigators (Barcelona)

Hospital Bellvitge: P. Cardona
Hospital Clínic: X. Urra
Hospital Germans Trias I Pujol: M. Millán
Hospital Vall d’Hebrón: M. Ribó

Collaborating Primary Stroke Centers (Catalan Stroke Program)

Hospital Josep Trueta (Girona)
Hospital Arnau de Vilanova (Lleida)
Hospital Joan XXIII (Tarragona)
Hospital Verge de la Cinta (Tortosa)
Hospital de Sant Pau (Barcelona)
Hospital Moisés Broggi (Barcelona)
Hospital Mutua de Tarrasa (Barcelona)

CT/CTA and MR/MRA Corelab

Andrew Demchuck (Calgary)
Mayank Goyal (Calgary)

Angiography Corelab
Rüdiger von Kummer (Dresden)

CRO: Anagram (Barcelona)

Data Management & Statistics: Bioclever (Barcelona)

Trial coordination office: E. López-Cancio (HGTiP, Barcelona)

Funding: Covidien Neurovascular (unrestricted grant)

Sponsor: Fundació Ictus (non-profit) (Barcelona)

* Biostatisticians