Randomized Trial Of Revascularization With Solitaire FR® Device Versus Best Medical Therapy In The Treatment Of Acute Stroke Due To Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours Of Symptom Onset

(REVASCAT - clinicalTrials.gov, NCT01692379)

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Disclosures

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- Sponsor: Fundació ICTUS (Non-profit foundation)
- Antoni Dávalos, MD: Consultancy fees (moderate) as member of the STAR steering committee

Why RevasCAT ?

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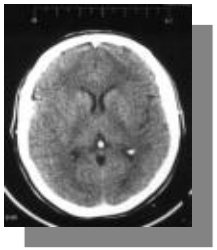
Levels of stroke care in Catalonia - 2010

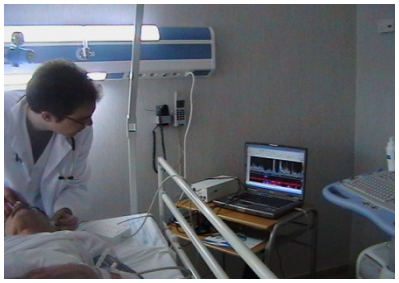
Community hospitals (n= 9/23 with telemedicine)

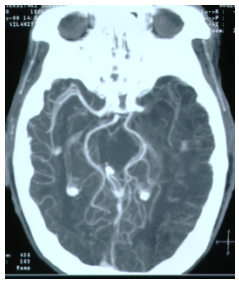


24h/d

+

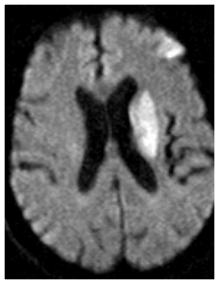
Primary stroke centers (n = 13)

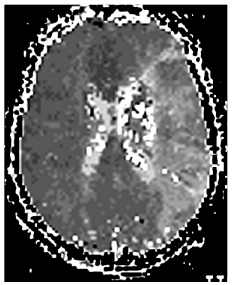


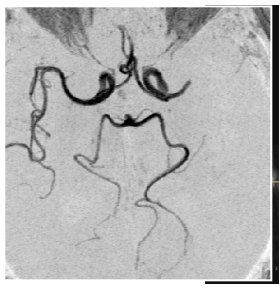


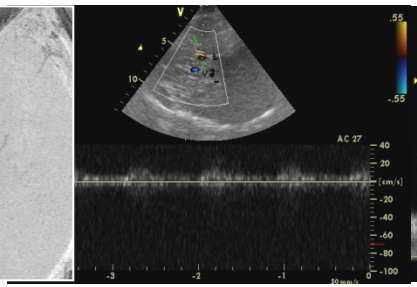
24h/d

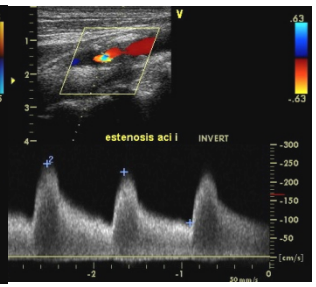
Comprehensive stroke centers (n = 5, 24h/7d)

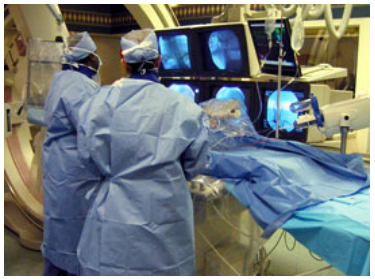




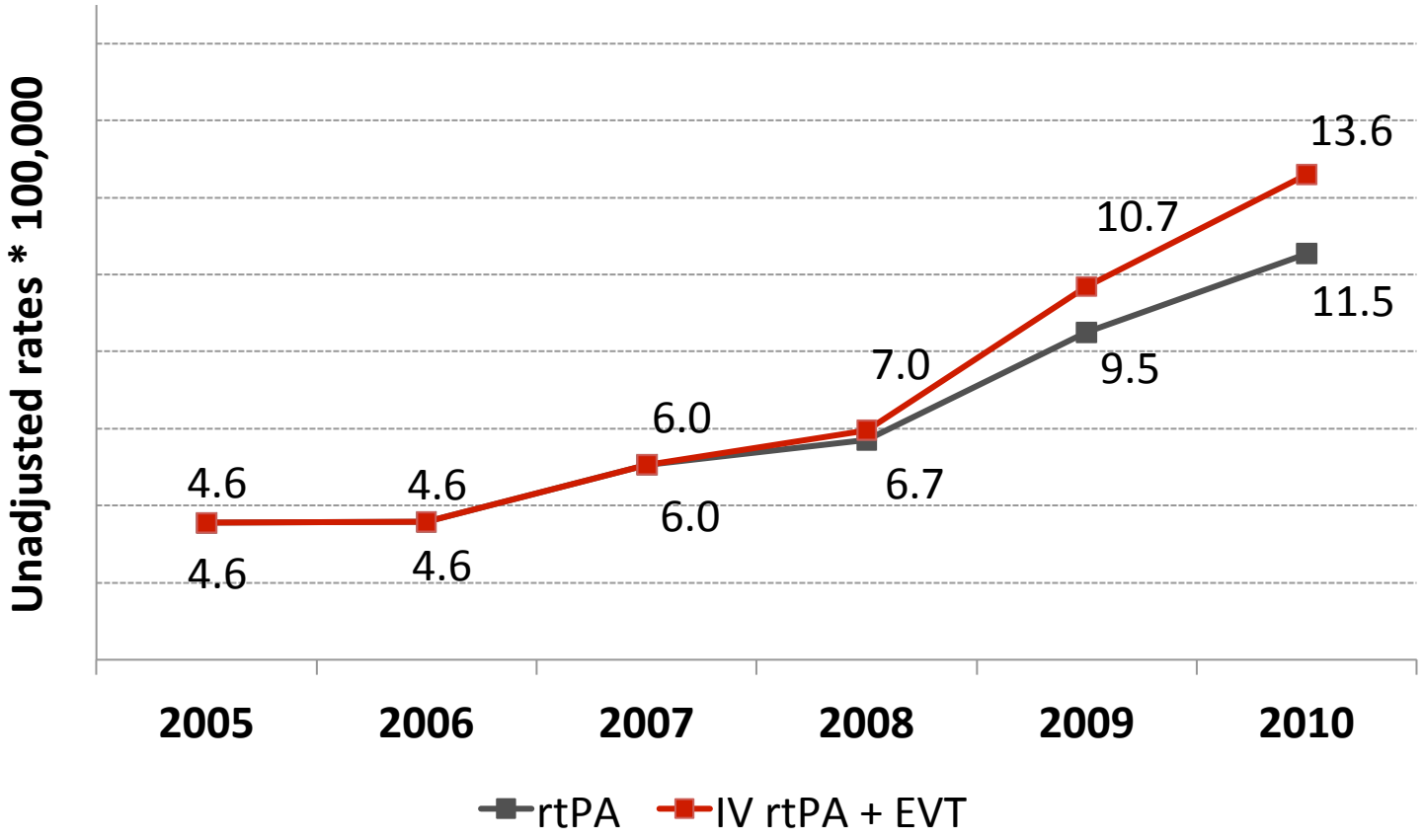








Overall reperfusion treatment rate (per 100,000 inhabitants-year) in Catalonia



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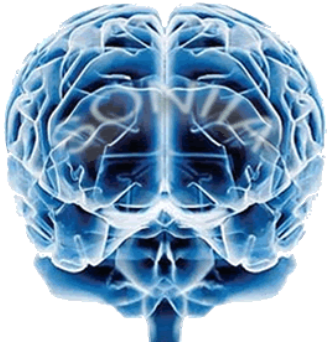

To perform a CONTINUOUS MONITORING of the **QUALITY** of ALL **REPERFUSION THERAPIES** administered to patients with acute ischaemic stroke within the **network of publicly financed acute hospitals** in Catalonia.

SONIIA

Period Jan-2011 to Nov-2012

536 patients

- ✓ 3 CH (TS connection)
- ✓ 7 PSC
- ✓ 6 CSC

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Clinical trial background

- General consensus on equipoise
- Wiliness to randomize all eligible patients
- Adequate patient population (7.5 million people)
- Adequate infrastructure (National Stroke Program, EMS, hospitals network)
- Uniform treatment modalities for treatment and control groups
- Reperfusion therapies concentrate in 4 CSC. Neurointerventional team available 24h
- Reperfusion therapies are consecutively and mandatory recorded in a central Register (**SONIIA**) that is monitored by the Health Department.

- **Potential advantages linked to a territorial design**
- Small homogeneous group of investigators & centers
- Potential exclusions from the target population will be known and monitored

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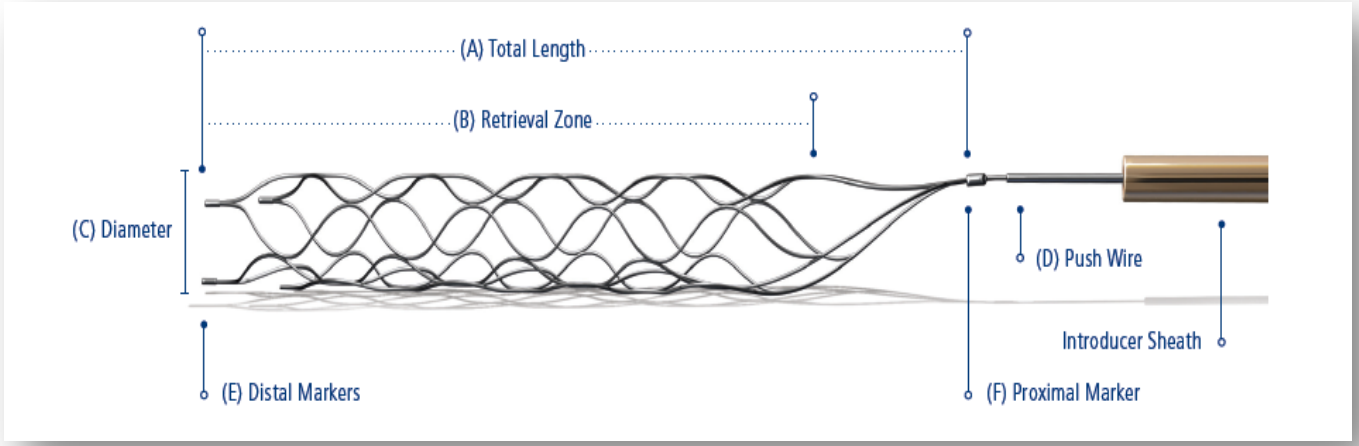
Study objective

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.



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

- Randomization is 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

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Primary efficacy endpoint

- Distribution of the modified Rankin Scale scores at 90 days (**shift analysis**) as evaluated by two separate assessors who are blinded to treatment.

Secondary efficacy endpoints

- Functional independence defined as mRS ≤ 2 at 90 days
- Dramatic favorable response (NIHSS improvement ≥ 8 or NIHSS of 0-2 at 24 hours)
- **Infarct volume on CT at 24 hours** evaluated by independent Corelab
- **Vessel recanalization on CTA or MRA at 24** hours adjudicated by a central Corelab
- **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
- Cost effectiveness analysis
- Comparison of the primary and secondary outcome endpoints between the trial control group 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).
- Procedural related complications and Serious Adverse Events (SAEs): groin hematoma, arterial perforation, arterial dissection, and embolization in a previously uninvolved vascular territory

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Inclusion criteria

- Acute ischemic stroke ineligible for IV thrombolysis or where patient has received IV thrombolytic therapy without recanalization after 30 min from tPA bolus
- 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 and tandem occlusions (proximal ICA + M1) **as evidenced by CTA, MRA**, or angiogram.
- Patient treatable (groin puncture) **within 8 hours** of symptom onset
- Informed consent

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Neuroimaging exclusion criteria

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

Molina C et al. Int J Stroke 2013 (in press)

Statistical design

- Maximum simple size 690 patients (effect size 10%, OR=1.615)
- Triangular model with 3 interim looks: 174, 346 and 518 patients completed
- Intention to treat shift analysis of the distribution of the modified Rankin Scale 0 to 5 scores at 90 days (mRS 5 and 6 will be equaled in the analysis) will be performed by Ordinal Logistic Regression accounting for the sequential design and considering minimization factors."

Probabilities of stopping at any interim under different scenarios for the treatment effect.

OLR grouping categories 5 and 6 (1000 simulations)													
		H0: OR=1			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
N	n	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.7%	0.3%	30.0%	0.4%	22.6%	23.0%	0.0%	50.2%	50.2%	0.0%	78.5%	78.5%
346	173	49.6%	0.6%	50.2%	2.1%	46.7%	48.8%	0.1%	43.1%	43.2%	0.0%	21.2%	21.2%
518	259	15.2%	1.0%	16.2%	2.3%	19.6%	21.9%	0.0%	6.3%	6.3%	0.0%	0.3%	0.3%
690	345	3.1%	0.5%	3.6%	1.5%	4.8%	6.3%	0.0%	0.3%	0.3%	0.0%	0.0%	0.0%
		97.6%	2.4%	100%	6.3%	93.7%	100%	0.1%	99.9%	100%	0.0%	100%	100%
Prob(N>518)		3.1%	0.5%	3.6%	1.5%	4.8%	6.3%	0.0%	0.3%	0.3%	0.0%	0.0%	0.0%
Fixed sample size			-			564			270			162	
Expected Ssize			335			366			272			211	

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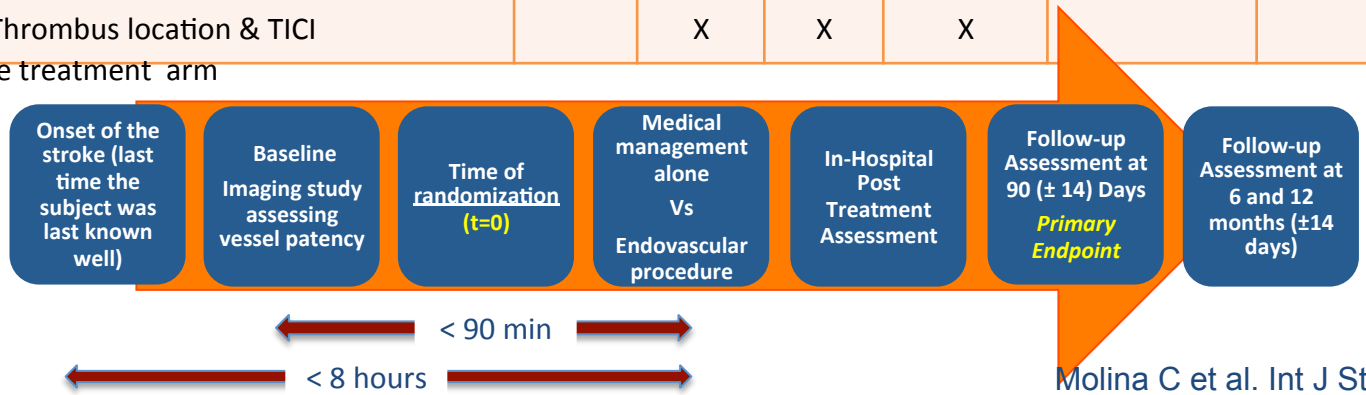
Schedule of key interventions and assessments

	Time point	Enrol-ment	Allo-cation	< 8 h	24 ± 12 h	5 ± 2 days or discharge	90 ± 14 days	1 year
Enrolment	Baseline details	X						
	Eligibility screen	X						
	Informed consent	X						
	Allocation (Trial website)		X					
Interventions	Best medical treatment	●	———	●				
	Angiogram[1]		X	X				
	Thrombectomy[1]			X				
	ASU or ICU admission		●	———	———	●		
Assessments	Modified Rankin Scale score	X					X	X
	NIHSS score	X	X		X	X	X	
	CT-CTA or DWI-MRA (CTP/PWI if >4.5h)	X			X			
	Thrombus location & TICI		X	X	X			

[1]Solitaire treatment arm



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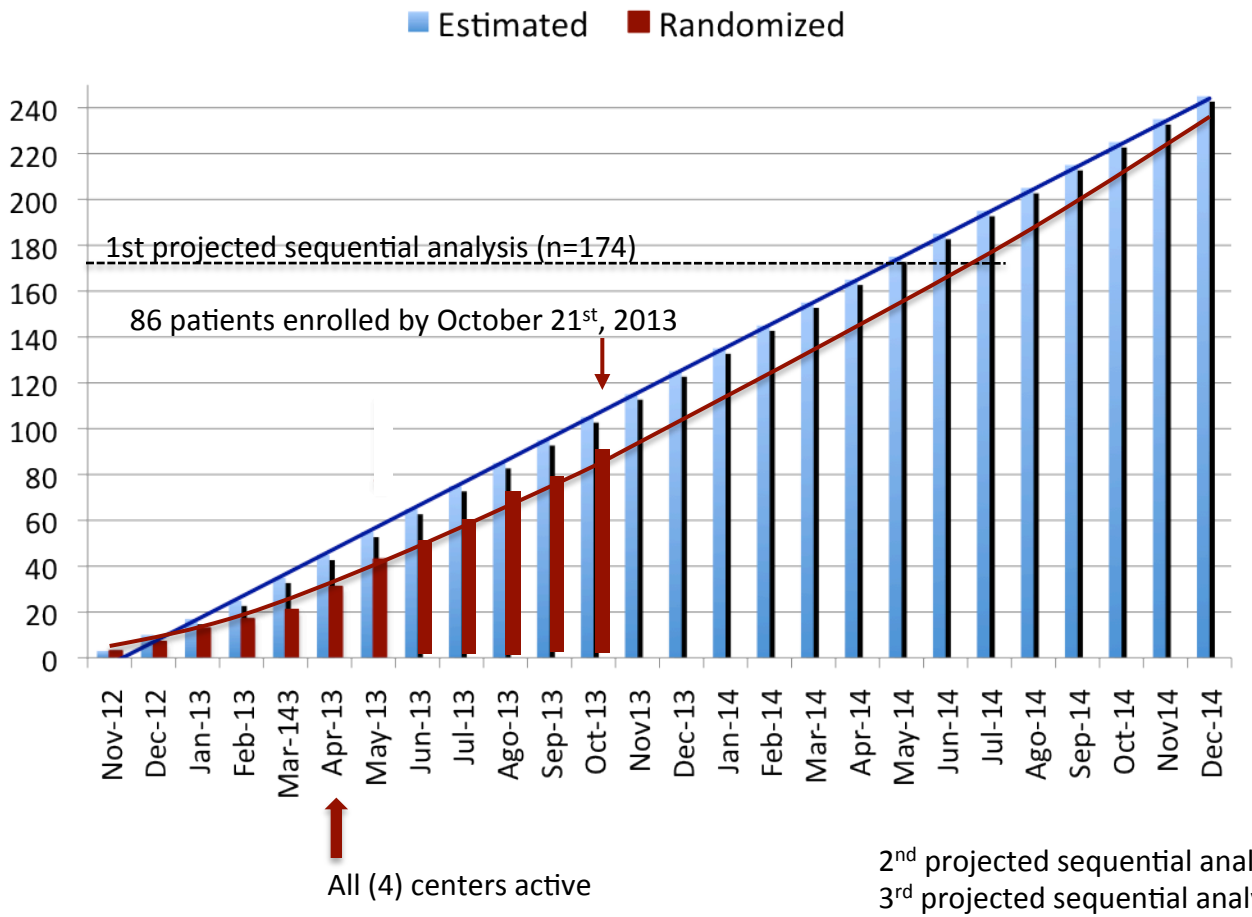
Procedure requirements

- 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)
- 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
- Sedation or intubation is discretional
- Angiographic images after deployment and retrieval for each pass and the time of each deployment must be recorded.

Current trial enrolment



2nd projected sequential analysis (n=346): Oct-2015
3rd projected sequential analysis (n=508):Jan-2017
Last projected interim analysis (n=690): Jun-2018

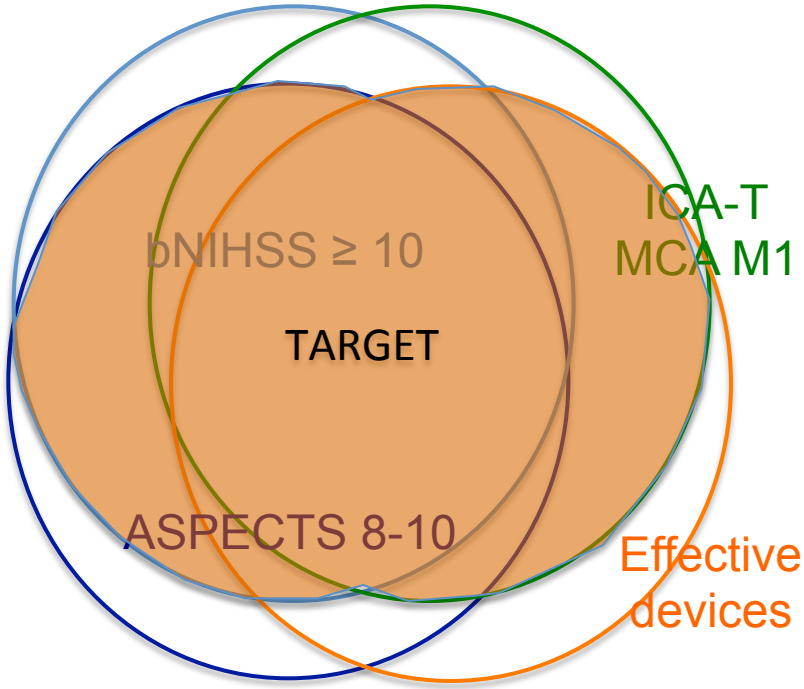
Updated from Dávalos A. ESC London 2013

Baseline clinical characteristics

	Retrospective	SWIFT (Rand SFR group only)	TREVO	TREVO 2 (Rand Trevo group only)	STAR	REVASCAT*
N	141	58	60	88	202	86
Age	66.3 ± 13.1	67.1 ± 12.0	65 (median)	67.4 ± 13.9	68.4 ± 12.5	64.6 ± 11.5
Male	56% (79/141)	48% (28)	45%	45%	40%	61.5%
Baseline NIHSS, median	18	18	18	19	17	17
ICA occlusion	28%	21%	21.7%	16%	18%	37.2% (intracranial ICA or tandem ICA +MCA-M1)
% VBA occlusions	11%	1.7%	8.3%	8%	N/A	0%
Time window <4.5h**						67.4%

- Minimization factors data updated by October 21st
- ** Time from onset to randomization

Trials of Endovascular Therapy in Acute Ischemic Stroke: How Can We Improve?



KEY POINTS FOR FUTURE TRIALS

1. Major vascular occlusion
2. Salvageable brain (penumbra)
3. Fast & effective revascularization
4. tPA eligible and non-eligible patients

Nogueira R, Gupta R and Davalos A. Stroke 2013 (online)

Acknowledgments

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