

**REVASCAT: A 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.**

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## ABSTRACT

REVASCAT is a multi-center, randomized, sequential and blinded-endpoint trial.

Subjects presenting with acute ischemic stroke within 8 hours from symptom onset and CT angiography (CT) or MR angiography (MRA) proven arterial occlusion of the internal carotid or proximal middle cerebral artery (MCA) (M1) who are either ineligible for intravenous IV alteplase or have received IV alteplase therapy without

recanalization will be randomized following a 1:1 ratio to receive mechanical

embolectomy with the CE MARK approved stentriever Solitaire™ FR revascularization device or medical management alone. The overall goal of the REVASCAT trial is to

establish whether subjects with a baseline NIHSS  $\geq 6$  and large artery occlusion of the anterior territory who can potentially undergo endovascular treatment within 8 hours

from the time last seen well have a more favorable outcome at 3 months as compared to subjects treated with standard medical therapy alone

The primary endpoint on the basis of intention-to-treat criteria will be the distribution of the modified Rankin Scale scores at 90 days. Sample size is projected to be 690 patients for an estimated common odds ratio of 1.615.

Randomization will be done under a minimization process using investigational center, age, baseline NIHSS, therapeutic window and vessel occlusion site. The study follows a sequential analysis (triangular model), with the first approach to test efficacy in 174 patients. If the study is continued at this point, further analyses will take place when data are available on 346, 518 and 690.

Salvageable brain will be evaluated by the Alberta Stroke Program Early CT score (ASPECTS) score on non-contrast CT or on diffusion-weighted MRI DWI-MRI.

Secondary endpoints are infarct volume evaluated on CT at 24 hours, dramatic early favorable response as determined by an National Institutes of Health Stroke Scale (NIHSS) of 0-2 or NIHSS improvement  $\geq 8$  points at 24 hours, vessel recanalization evaluated by CTA or MRA at 24 hours in both treatment groups and successful

recanalization in the Solitaire arm according to the Thrombolysis in Cerebral Infarction (TICI) classification assessed by TICI (Thrombolysis in Cerebral Infarction) 2b or 3 on the post-procedure angiogram adjudicated by a central core-lab.

Safety variables will be mortality at 90 days, symptomatic intracranial hemorrhage (ICH) rates at 24 hours and procedural related complications: arterial perforation, arterial dissection, and embolization in a previously uninvolved vascular territory adjudicated by an independent committee.

## BACKGROUND

Intravenous thrombolysis remains the only approved therapy for acute ischemic stroke. However, it has a short therapeutic window, a strong time-dependency, and has only marginal benefit in strokes due to proximal arterial occlusions (1,2). Endovascular therapy has many theoretic advantages over iv thrombolysis. Mechanical thrombectomy reduces and may even preclude the use of chemical thrombolytics and this may further reduce the risk of ICH, allowing faster and sustained recanalization. However, endovascular recanalization techniques have also relevant disadvantages, including delays in initiating treatment, complexity of the procedure, high level of required technical expertise, low availability and risks and expense of an invasive procedure as compared with iv tPA.. Nevertheless, given the strong relationship between vessel recanalization and good clinical outcomes, the advantages of endovascular stroke therapy as the most efficacious treatment for recanalization of large vessel intracranial occlusions may outweigh its disadvantages and risks, but this needs yet to be proved.

Novel stent retrievers or “stentriever”, intracranial stents that are deployed and retrieved snaring the thrombus showed very promising results (3,4). Recently, the SOLITAIRE™ With the Intention for Thrombectomy (SWIFT) trial compared two mechanical thrombectomy devices: The MERCI retriever and the SOLITAIRE

retrievable stent in the arterial recanalization of patients with acute ischemic stroke (5). The SWIFT trial has shown in 113 patients that the Solitaire™ FR device is superior to the MERCI® Retriever in achieving successful revascularization (by Corelab, 68% vs 30%,  $p < 0.001$ ), inducing less symptomatic intracranial hemorrhage (2% vs 11%,  $p = 0.06$ ), reducing mortality (17% vs 38%,  $p = 0.02$ ), and increasing good neurologic outcome 3 months after stroke (58% vs 33%). TREVO® Retrieval System has also shown a high rate of revascularization and favorable results (6). Results of the recently reported TREVO 2 trial (7) confirmed the superiority of stentriever over Merci embolectomy with respect to recanalization rates (TICI $\geq$ 2 in 86.4 vs 60% respectively,  $p < 0.00001$ ), clinical outcomes (mRS $\leq$ 2 in 40% vs 21.8% respectively,  $p = 0.01$ ) and with no significant difference in the risk of SIHC (6.8% vs 8.9% respectively,  $p = 0.78$ ). A recently published single-center comparison between Merci and Trevo/Solitaire showed similar results, with even significant difference in the SIHC rate (TICI 2b-3 82 vs 62%,  $p = 0.016$ , mRS $\leq$ 2 65 vs 35%,  $p = 0.002$  and SIHC 10 vs 28%,  $p = 0.01$ ) (8). In none of the aforementioned trials, multimodal imaging showing tissue at risk was used for patient's selection.

The IMS-3 was a phase III, randomized, multi-center, open label, 900 subject clinical trial conducted to examine whether a combined intravenous (IV) and intra-arterial (IA) approach to recanalization was superior to standard IV rt-PA alone when initiated within three hours of acute ischemic stroke onset (9). The trial was prematurely halted due to futility according to the results of a pre-specified interim analysis. **The proportion of patients who achieved a mRS score mRS $\leq$ 2 at 90 days did not differ significantly according to treatment (40.8% with endovascular therapy and 38.7% with intravenous t-PA; Findings in the endovascular-therapy and intravenous t-PA groups were similar for mortality at 90 days (19.1% and 21.6%, respectively;  $P = 0.52$ ) and the proportion of patients with symptomatic intracerebral hemorrhage within 30 hours after initiation of t-PA (6.2% and 5.9%, respectively;  $P = 0.83$ ).**

Of note, different intraarterial approaches and devices were allowed during the trial and patients were randomized after the initiation of IV tPA without knowledge of vessel status. Therefore, there is equipoise on endovascular therapy for acute stroke so far. The ideal thrombectomy trial design should test a single device, randomize patients according to intracranial occlusion, include tPA non-responders and use advanced imaging for patients selection beyond 4.5 hours. In addition, the trial should be conducted in a few centres with high recruitment capacity and neurointerventional expertise to decrease intercentre variability.

Following this approach, the overall goal of the REVASCAT trial is to establish whether subjects with a baseline NIHSS  $\geq 6$  and large artery occlusion of the anterior territory who can potentially undergo endovascular treatment within 8 hours from the time last seen well have a more favorable outcome at 3 months as compared to subjects treated with standard medical therapy alone.

## **METHODS**

### **Study design and participants**

REVASCAT is a multi-center, randomized, sequential and blinded-endpoint trial. The randomization employs a 1:1 ratio of mechanical embolectomy with approved stentriever Solitaire FR® versus standard medical management alone.

### ***Eligibility Criteria***

1. Patients with acute ischemic stroke ineligible for IV thrombolytic treatment (e.g., subject presents beyond recommended time from symptom onset), or treated with IV thrombolytic therapy without recanalization after a minimum of 30 min from start of iv tPA infusion
2. Occlusion (TICI 0-1) of the intracranial ICA (distal ICA or T occlusions), MCA-M1 segment or tandem proximal ICA/MCA-M1 suitable for endovascular treatment, as

evidenced by CTA, MRA or angiogram, with or without concomitant cervical carotid occlusion or stenosis.

3. Patient treatable within 8 hours from time last seen well at baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their “onset” at beginning of sleep)

4. Age  $\geq 18$  and  $\leq 80$

5. Baseline NIHSS score must be equal or higher than 6 points

6. No significant pre-stroke functional disability (mRS  $\leq 1$ )

7. Informed consent obtained from patient or acceptable patient surrogate

### ***Exclusion Criteria***

#### *Clinical*

1. Known hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR  $> 3.0$

2. Baseline platelet count  $< 30.000/\mu\text{L}$

3. Baseline blood glucose of  $< 50\text{mg/dL}$  or  $>400\text{mg/dl}$

4. Severe, sustained hypertension (SBP  $> 185$  mm Hg or DBP  $> 110$  mm Hg)

5. Patients in coma (NIHSS item of consciousness  $>1$ ) (Intubated patients for transfer could be randomized only in case an NIHSS is obtained by a neurologist prior transportation).

6. Seizures at stroke onset which would preclude obtaining a baseline NIHSS

7. Serious, advanced, or terminal illness with anticipated life expectancy of less than one year.

8. History of life threatening allergy (more than rash) to contrast medium

9. Subjects who have received iv t-PA treatment beyond 4,5 hours from the beginning of the symptoms.

10. Renal insufficiency with creatinine  $\geq 3$  mg/dl

11. Woman of childbearing potential who is known to be pregnant or lactating or who has a positive pregnancy test on admission.

12. Subject participating in a study involving an investigational drug or device that would impact this study.

13. Cerebral vasculitis

14. Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations; mRS score at baseline must be  $\leq 1$ .

15. Unlikely to be available for 90-day follow-up

### *Neuroimaging*

16. Hypodensity on CT or restricted diffusion amounting to an ASPECTS score of  $<7$  on non-contrast CT, or  $<6$  on DWI MRI. ASPECTS may be also evaluated by cerebral blood flow (CBV) maps of CT Perfusion, or CTA source imaging (CTA-SI) in patients whose vascular occlusion study (CTA/MRA) confirming qualifying occlusion, is performed beyond 4.5 hours of last seen well.

17. CT or MR evidence of hemorrhage (the presence of microbleeds is allowed).

18. Significant mass effect with midline shift.

19. Evidence of ipsilateral carotid occlusion, high grade stenosis or arterial dissection in the extracranial or petrous segment of the internal carotid artery *that cannot be treated* or will prevent access to the intracranial clot or excessive tortuosity of cervical vessels precluding device delivery/deployment

20. Subjects with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation)

21. Evidence of intracranial tumor (except small meningioma).

### **Randomization**

A "Real-Time" randomization procedure is implemented via the REVASCAT Trial Website. First, the clinical center investigator enters the basic baseline and eligibility information of a subject. If the subject's eligibility status is confirmed, the server allocates the treatment on the basis of a minimization process to balance in a 1:1 ratio the 2 groups both overall as well as within every category of the factors:

investigational center, age ( $\leq 70$  or  $> 70$  years), baseline NIHSS (6-16 or  $\geq 17$ -or more), therapeutic window ( $\leq 4.5$  or  $> 4.5$  hours), and occlusion site (intracranial ICA or M1 segment).

## **Treatment**

Vascular neurologists and trained interventional neuroradiologists or neurologists in certified comprehensive stroke centres that treat more than 500 acute stroke patients and perform more than 60 acute mechanical thrombectomies every year will treat patients. Neurointerventionalists must have previously performed at least 20 thrombectomies with Solitaire device in acute ischemic stroke patients. Patients in both arms will be admitted at acute stroke units (or ICU if needed) and treated following the European Stroke Organization ESO guidelines (ESO Cerebrovasc Dis 2008).

All interventional therapy must be started earlier than eight hours relative to the time the subject was last seen well. Treatment initiation is defined as groin puncture. The duration of the interventional procedure should not exceed three hours. To allow an intention to treat interpretation, no crossover is permitted.

Endovascular therapy in the REVASCAT will adhere strictly to the following treatment principles:

1. Only the Solitaire FR device will be allowed in REVASCAT.
2. If the Solitaire device fails after a maximum of **six** passes per vessel, no pharmacological or other mechanical rescue therapies will be allowed.
3. Systemic anticoagulation may not be used other than in the heparinized saline infusion as per local interventional procedure standards.
4. Balloon angioplasty and/or stenting of extracranial ICA in cases with ICA/M1 tandem occlusions will be allowed as per site specific protocols. For sites that perform stenting in addition to angioplasty for tandem occlusions, it is recommended that aspirin 300 mg



and clopidogrel load (600 mg) are administered orally or via nasogastric tube prior to intervention if possible

5. Angioplasty and/or stenting of intracranial vessels beyond the petrous segment of the ICA will not be allowed.

6. The use of a balloon guide catheter in the proximal ICA is highly recommended but optional and solely at the discretion of the interventionalist. The rationale for using the balloon guide catheter is to prevent distal embolization including in previously uninvolved territories during device and clot retrieval.

### **Efficacy endpoints**

#### *Primary endpoint*

The primary endpoint will be the distribution of the modified Rankin Scale scores at 90 days (shift analysis) as evaluated following a structured interview by two separate certified assessors who will be blinded to treatment.

#### *Clinical secondary endpoints*

1. Early response to treatment as determined by a NIHSS drop of  $\geq 8$  or NIHSS 0-2 at 24 (-2/12) hours from randomization or before discharge if patient is discharged prior to the above time limit

2. Barthel Index at 90 days

3. NIHSS at 90 days

4. mRS score (0-2 versus 3-6) at 12 months

5. Trail Making Test at 90 days

6. Quality of life measured by EuroQol EQ-5D at 90 days and 12 months

7. Cost effectiveness analysis

8. Secondary analyses of the primary endpoint: Functional independence defined as mRS  $\leq 2$  at 90 days and severe dependence defined as mRS  $> 3$  at 90 days

#### *Neuroimaging secondary endpoints*

1. Final infarct volume measured on 24 (-2/12) hours CT (MRI's if available will be used in a separate analysis).
2. Median modified ASPECTS score increase defined as CT ASPECTS score at 24 hours minus baseline ASPECTS score.
3. Vessel recanalization evaluated by CT angiography or MRA at 24 (-2/12) hours in both treatment groups
4. Immediate Post-Endovascular Treatment Recanalization (for the mechanical embolectomy group group only). Successful recanalization is defined as TICl (Thrombolysis in Cerebral Infarction) 2b or 3 in the post-procedure angiography.

### **Safety end-points**

1. Clinically significant ICH rates at 24 (-2/+12) hours. All intracerebral hemorrhages will be classified by a central core-lab using the ECASS criteria. Symptomatic ICH will be defined as per the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition: deterioration in NIHSS score of  $\geq 4$  points within 24 hours from treatment and evidence of intraparenchymal hemorrhage type 2 in the 22 to 36 hours follow-up imaging scans. The incidence of any asymptomatic hemorrhage measured at 24 (-2/+12) hours will also be compared at day 90
2. Mortality at day 90.
3. Procedural related complications: arterial perforation, arterial dissection, impossibility to retrieve the stent, and embolization in previously uninvolved vascular territory

### **Masking**

Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 ( $\pm 12$ ) hours, 5 ( $\pm 2$ ) days or prior to discharge if discharge occurs before 3 days and at 3 months who can remain blinded to the treatment of each subject. Data entry would

not reveal the study arm assignment and patients will be instructed to minimize the chance of disclosing their treatment group to the evaluator.

Regarding the primary endpoint, first, a local independent neurologist, not involved in the trial patient management, will record the mRS score in a face to face clinical visit; and second, an experienced nurse will centrally evaluate mRS score by telephone call, recording the interview in an audio-tape. In case of disagreement between the two assessors, a centralized neurologist will rate mRS by using the audio-tape recording and his mark will be the primary endpoint value in this case. All of them will directly introduce mRS score in the database without access to any further information.

All neuroimaging secondary endpoints including recanalization at 24 hours, infarct volume and hemorrhage will be determined by the CT/MR core lab which will be also blinded to treatment allocation. Successful recanalization in the post-procedure angiography in the mechanical embolectomy group will be classified by a specific core-lab.

Serious adverse events (SAEs) will be adjudicated by one member of the independent Clinical Events Committee that will be blinded to treatment arm, and procedural related complications will be adjudicated by one member that will be unmasked.

#### **Data safety monitoring board (DSMB)**

The purpose of the DSMB is to review, on a regular basis, unmasked accumulated efficacy and safety data. The DSMB will be composed of three stroke neurologists or interventionalists, and a statistician who are not participating in the study and are not affiliated with the sponsor. Members of the DSMB are listed in the appendix. The role of the DSMB will be to: 1) make recommendations to the Executive Committee regarding stopping or extending the trial based on the pre-planned efficacy interim analysis; and 2) review the occurrence of AEs and make recommendations to the Executive Committee regarding safety of the study.

### **Imaging Core Lab**

Centralized imaging core labs will be used in this study to provide consistent evaluation of images. Two independent central imaging core labs will be established to independently review CT/MR and angiographic images. One lab will review angiographic images from the procedure to determine clot location and revascularization. Another independent core lab will review CT/MR images obtained at baseline and at 24 hours for confirmation of inclusion criteria (occlusion of the intracranial ICA and/or MCA-M1 with or without concomitant cervical carotid occlusion or stenosis; ASPECTS score), and presence/absence of hemorrhage, vessel patency and infarct volume at 24 (-2/+12) hours. Having a CT/MR core lab independent from the angiographic core lab ensures that the CT/MR core lab is blinded to the treatment. Each core lab will use standardized procedures for neuroimaging evaluation defined in a specific manual. They will provide no information to the investigators with the exception of the deviations from the neuroimaging inclusion criteria.

### **Clinical Events Committee (CEC)**

A CEC will be in place for the study using a minimum of 2 physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study. The CEC will be comprised of individuals who are independent of the investigational sites. This committee will be responsible for the review and validation of all complications that occur over the course of the study and the subsequent classification of these complications as related to the device or procedure.

Members of the CEC will review all complications and adjudicate them as defined in the Adverse Event section in the CEC Manual of Operations. The CEC can request additional source documentation and any imaging obtained in support of the adverse event to assist with adjudication.

## **Statistical design**

### **Effect size measure and primary endpoint analysis.**

We expect that the effect of the revascularization will improve patient status for the first 5 mRS possible cut-points, but not for the change between 5 and 6. In other words, the intervention may “shift” patients to minor values from 5 to 4; from 4 to 3, from 3 to 2; from 2 to 1 and from 1 to 0, but not from 6 to 5. Furthermore, the order preference between those two values, severe disability and death, is not clear neither for patients, clinicians, nor care providers (10). The Ordinal Logistic Analysis (OLR) based on cumulative logits provides a treatment effect in the form of a common estimate of the OR for improvement over considered cut-points. This analysis has been shown to be robust for minor deviations of the assumption of a common OR underlying behind any cut-point (11). This logistic regression will adjust both for the minimization factors and for the interventionist.

### **Interim analyses rationale**

We desired a maximum of 4 looks when approximately 25, 50, 75 and 100% of the sample sizes finish the follow-up, 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 device procedure or because of the futility of the trial. We were not interested in proving that the test intervention was inferior to the best medical treatment.

At interim analysis, in case the stopping boundaries are crossed, the DSMB may recommend stopping the study either for efficacy or for futility. When addressing safety, DSMB will also consider mortality (mRS=6) and severe dependency (mRS=5) at 3 months as one single value. In case of early stopping, any over-running patient will be followed until the end of the study and a final analysis will be performed.

### **Devised effect, power and sample size.**

The expected proportions of patients having a mRS score 0 or 1 at 90 days are 25% and 35% in the control and treated arms. This results in an expected OR of 1.615. The

trial was designed to have 90% chances to conclude efficacy in the case of a clinical advantage of a common OR of 1.615 through any possible mRS cut-points (including 5 to 6) and an overall 2.5% one-sided risk of concluding efficacy in case of no effect.

After a search (12) a triangular test with 3 interim looks plus 1 final analysis was specified with values  $a = 2.18074$  and  $v1 = 14.008681$ . The total maximum sample size was 690.

The trials proprieties for the final analysis, pooling mRS values 5 and 6, were validated by simulation including two higher hypothetical OR: 2.00 (15%: 40 over 25% on the 0 or 1 versus 2 to 6 cut-point) and 2.45 (20%: 45 over 25%). Three hypothetical different scenarios (figures 1 to 3) for the treatment effect were analysed: (A) the targeted studied effects (1,615; 2,000 and 2,450) applies exactly to the 6 frontiers or cut-point on the 0 to 6 ranking scale; (B) as before, but the targeted effects are constant for the 5 first frontiers and they are diluted in the last 5 to 6 cut-point resulting in a diluted overall estimate (common along the 6 overall possible frontiers); and (C) as before, but now the diluted overall estimate fits the targeted effects.

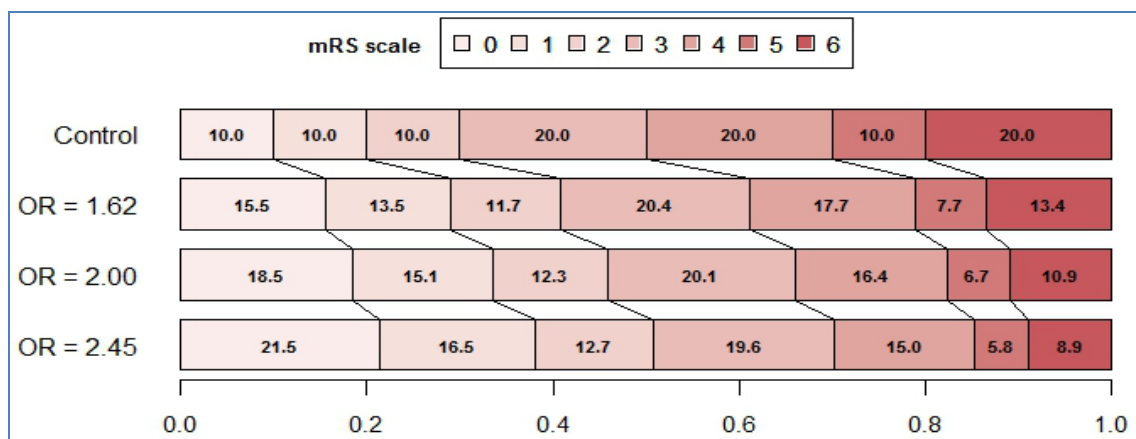


Figure 1: In scenario **A**, the same OR (either 1.62; 2.00 and 2.45) applies to any possible cut-point.

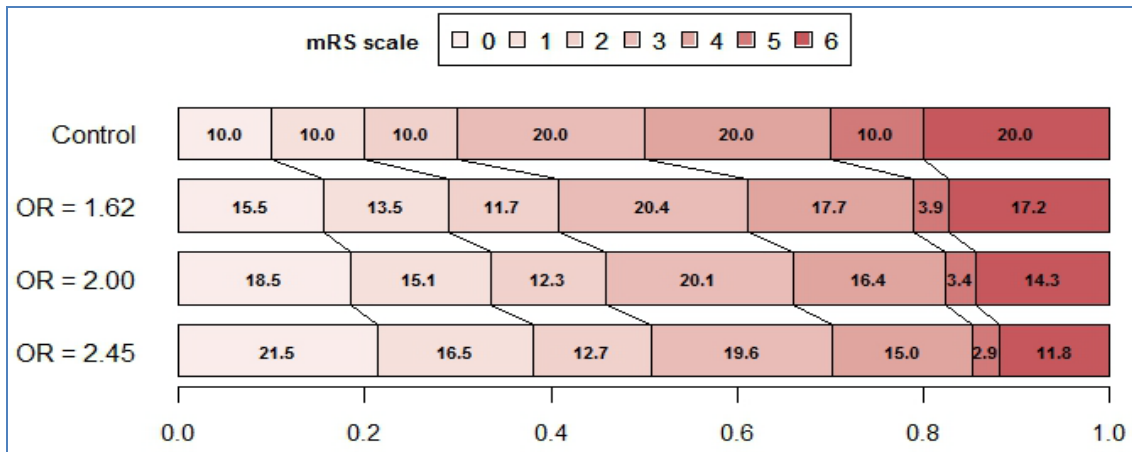


Figure 2: In scenario **B**, the same OR (1.62; 2.00 and 2.45) applies only to the first 5 cut-points, and it is diluted in the last 5 to 6 frontier. As a consequence, the common (“averaged”) OR estimated through all cut-points, including the 5 to 6 frontier is smaller.

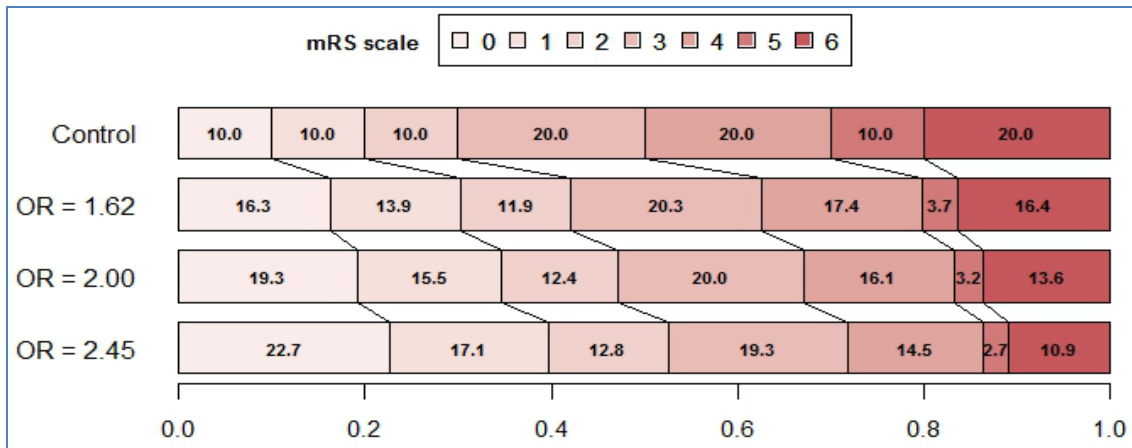


Figure 3: In scenario **C**, again, the same OR applies to the first 5 cut-points and it is diluted in the last 5 to 6 frontier; but now the common averaged OR results in an estimate of 1.62; 2.00 and 2.45.

On those three scenarios, two analysis strategies were compared: considering the full mRS scale with the 6 possible cut-points versus just 5 (after pooling values 5 and 6). As it was expected, both analyses performed better on the scenarios where their assumptions better hold: the first analysis on scenario A (with almost negligible differences), and the second on B and C (with more relevant advantages). As scenarios B and C are both more realistic and more desired for patients and care providers, the analysis pooling values 5 and 6 was chosen as the final analysis. Its power on the 3 considered scenarios (87.7%, 88.8% and 93.7%) was considered reasonable by the steering committee.

OLR without grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1 ( $\Delta = 0$ )			H1: OR=1.62 ( $\Delta = 0.10$ )			H1: OR=2 ( $\Delta=0.15$ )			H1: OR =2.45 ( $\Delta=0.2$ )		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.1%	0.5%	29.6%	1.2%	18.0%	19.2%	0.0%	42.4%	42.4%	0.0%	70.0%	70.0%
346	173	49.6%	0.9%	50.5%	3.2%	41.6%	44.8%	0.3%	47.7%	48.0%	0.0%	29.5%	29.5%
518	259	16.0%	0.7%	16.7%	4.7%	20.4%	25.1%	0.1%	8.6%	8.7%	0.0%	0.5%	0.5%
690	345	2.9%	0.3%	3.2%	2.2%	8.7%	10.9%	0.0%	0.9%	0.9%	0.0%	0.0%	0.0%
Prob(N>518)		97.6%	2.4%	100%	11.3%	88.7%	100%	0.4%	99.6%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			394			291			226		

OLR grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.7%	0.3%	30.0%	1.2%	17.6%	18.8%	0.0%	42.4%	42.4%	0.0%	69.8%	69.8%
346	173	49.6%	0.6%	50.2%	3.9%	40.1%	44.0%	0.4%	46.7%	47.1%	0.0%	29.6%	29.6%
518	259	15.2%	1.0%	16.2%	5.2%	22.0%	27.2%	0.1%	9.4%	9.5%	0.0%	0.6%	0.6%
690	345	3.1%	0.5%	3.6%	2.0%	8.0%	10.0%	0.0%	1.0%	1.0%	0.0%	0.0%	0.0%
Prob(N>518)		97.6%	2.4%	100%	12.3%	87.7%	100%	0.5%	99.5%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			395			293			227		

Discrepancies													
N	n	H0: OR=1			H1: OR=1.62			H0: OR=2			H1: OR=2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	0.6%	-0.2%	0.4%	0.0%	-0.4%	-0.4%	0.0%	0.0%	0.0%	0.0%	-0.2%	-0.2%
346	173	0.0%	-0.3%	-0.3%	0.7%	-1.5%	-0.8%	0.1%	-1.0%	-0.9%	0.0%	0.1%	0.1%
518	259	-0.8%	0.3%	-0.5%	0.5%	1.6%	2.1%	0.0%	0.8%	0.8%	0.0%	0.1%	0.1%
690	345	0.2%	0.2%	0.4%	-0.2%	-0.7%	-0.9%	0.0%	0.1%	0.1%	0.0%	0.0%	0.0%

Table 1: Results for both analyses in scenario A, as well as their difference.

OLR without grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1 ( $\Delta = 0$ )			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.1%	0.5%	29.6%	1.7%	13.6%	15.3%	0.0%	37.8%	37.8%	0.0%	67.5%	67.5%
346	173	49.6%	0.9%	50.5%	4.4%	37.2%	41.6%	0.1%	49.4%	49.5%	0.0%	30.9%	30.9%
518	259	16.0%	0.7%	16.7%	5.0%	24.2%	29.2%	0.3%	11.2%	11.5%	0.0%	1.6%	1.6%
690	345	2.9%	0.3%	3.2%	4.0%	9.9%	13.9%	0.1%	1.1%	1.2%	0.0%	0.0%	0.0%
Prob(N>518)		97.6%	2.4%	100%	15.1%	84.9%	100%	0.5%	99.5%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			418			305			233		

OLR grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.7%	0.3%	30.0%	1.3%	16.6%	17.9%	0.0%	41.2%	41.2%	0.0%	70.6%	70.6%
346	173	49.6%	0.6%	50.2%	3.5%	41.0%	44.5%	0.0%	48.1%	48.1%	0.0%	28.2%	28.2%
518	259	15.2%	1.0%	16.2%	3.2%	24.4%	27.6%	0.3%	9.6%	9.9%	0.0%	1.2%	1.2%
690	345	3.1%	0.5%	3.6%	3.2%	6.8%	10.0%	0.1%	0.7%	0.8%	0.0%	0.0%	0.0%
Prob(N>518)		97.6%	2.4%	100%	11.2%	88.8%	100%	0.4%	99.6%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			397			295			227		

Discrepancies													
N	n	H0: OR=1			H1: OR=1.62			H0: OR=2			H1: OR=2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	0.6%	-0.2%	0.4%	-0.4%	3.0%	2.6%	0.0%	3.4%	3.4%	0.0%	3.1%	3.1%
346	173	0.0%	-0.3%	-0.3%	-0.9%	3.8%	2.9%	-0.1%	-1.3%	-1.4%	0.0%	-2.7%	-2.7%
518	259	-0.8%	0.3%	-0.5%	-1.8%	0.2%	-1.6%	0.0%	-1.6%	-1.6%	0.0%	-0.4%	-0.4%
690	345	0.2%	0.2%	0.4%	-0.8%	-3.1%	-3.9%	0.0%	-0.4%	-0.4%	0.0%	0.0%	0.0%

Table 2: Results for both analyses in scenario B, as well as their differences.



OLR without grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	29.1%	0.5%	29.6%	0.7%	19.2%	19.9%	0.1%	46.2%	46.3%	0.0%	75.3%	75.3%
346	173	49.6%	0.9%	50.5%	2.9%	44.6%	47.5%	0.2%	45.5%	45.7%	0.0%	24.3%	24.3%
518	259	16.0%	0.7%	16.7%	3.1%	21.4%	24.5%	0.0%	7.6%	7.6%	0.0%	0.4%	0.4%
690	345	2.9%	0.3%	3.2%	2.2%	5.9%	8.1%	0.0%	0.4%	0.4%	0.0%	0.0%	0.0%
Prob(N>518)		97.6%	2.4%	100%	8.9%	91.1%	100%	0.3%	99.7%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			382			281			217		

OLR grouping categories 5 and 6 (1000 simulations)													
N	n	H0: OR=1			H1: OR=1.62			H1: OR=2			H1: OR =2.45		
		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%
Prob(N>518)		97.6%	2.4%	100%	6.3%	93.7%	100%	0.1%	99.9%	100%	0.0%	100%	100%
Fixed sample size		-			564			270			162		
Expected Ssize		335			366			272			211		

Discrepancies													
N	n	H0: OR=1			H1: OR=1.62			H0: OR=2			H1: OR=2.45		
		Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both	Futility	Positive	Both
174	87	0.6%	-0.2%	0.4%	-0.3%	3.4%	3.1%	-0.1%	4.0%	3.9%	0.0%	3.2%	3.2%
346	173	0.0%	-0.3%	-0.3%	-0.8%	2.1%	1.3%	-0.1%	-2.4%	-2.5%	0.0%	-3.1%	-3.1%
518	259	-0.8%	0.3%	-0.5%	-0.8%	-1.8%	-2.6%	0.0%	-1.3%	-1.3%	0.0%	-0.1%	-0.1%
690	345	0.2%	0.2%	0.4%	-0.7%	-1.1%	-1.8%	0.0%	-0.1%	-0.1%	0.0%	0.0%	0.0%

Table 3: Results for both analyses in scenario C, as well as their differences.

In case of missing scale value and successful contact with patients or relatives, last observation scale value will be carried forward. Worst scale values will be assigned to any documented death or non-successful contact.

### Secondary efficacy analyses.

To check the consistency of the results under hypothetical unmasking of the local assessor of mRS, the primary analysis will be repeated for the central mRS evaluator. As less reliability is expected for a single ratter, concordance will be based on point and interval estimates and non in significant p values.

The common cumulative OR assumption of the modified Rankin scale will be visually evaluated and estimates for any possible cut-point will be also provided. Comparison of the primary and secondary outcome endpoints between the trial control group and patients treated with endovascular reperfusion therapies outside the REVASCAT trial will provide information of external validity. The prospective population-based SONIIA

database of all cases treated in Catalunya with reperfusion therapies allows performing this analysis. The consistency of the results under alternative missing value assumptions will also be studied (13).

A fully specified statistical analysis plan will be approved by the steering committee before first interim.

### **Analysis of Safety Endpoints**

Mortality at 90 days will be assessed for all enrolled subjects. A Kaplan-Meier analysis will be done and the mortality rate in each arm at 90 days with accompanying 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.

There is currently no standard for defining clinically significant or symptomatic ICH that is universally accepted. Thus, in addition to the definition above, it is anticipated that in the final analysis, other alternative definitions for symptomatic ICH may also be used and analyzed separately for comparison with other studies and historical literature (e.g., NINDS, ECASS III, MultiMERICI). The CEC will be tasked with defining the criteria to be used in the primary analysis of symptomatic ICH.

A descriptive analysis of study-defined adverse events will be presented in aggregate and by event. The rates and 95% exact Clopper-Pearson confidence intervals will be provided.

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