PROTOCOLE DE RECHERCHE BIOMEDICALE

Combined use of contact aspiration and the stent retriever technique versus stent retriever alone for recanalisation in acute cerebral infarction: the randomized ASTER2 study

Acronyme : Aster 2

VERSION 3 of 12 October 2017

SPONSOR :	**PRINCIPAL INVESTIGATOR :**
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☐ **Etude monocentrique** ☒ **Etude multicentrique**

Abbreviations

AIS	Acute Ischemic Stroke
IV-tPA	Intravenous tissue plasminogen activator
NIHSS	National Institutes of Health Stroke Scale
IAT	Intra-arterial thrombectomy
LVO	Large vessel occlusion
TICI	Thrombolysis in cerebral infarction
ENT	Emboli to new territory
SAE	Serious adverse event
SR	Stent retriever
AOL	Arterial Occlusive Lesion

HOPITAL FOCH

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1 Study Synopsis:

Full title	Combined use of contact aspiration and the stent retriever technique versus stent retriever alone for recanalisation in acute cerebral infarction : the randomized ASTER2 study
Acronym	ASTER2
Coordinating Investigator	Dr Bertrand Lapergue
Sponsor	Hospital Foch, Suresnes
Scientific justification	Mechanical thrombectomy (MT) with a stent retriever (SR) device is now the standard intervention in ischemic stroke with large vessel occlusion. Favorable outcome is strongly associated with the successful reperfusion status. New device of MT such as contact aspiration seems promising to increase reperfusion status and clinical outcome
Primary objective and assessment criterion	The main hypothesis is to show the superiority of combining the use of contact aspiration with a stent retriever compared to a stent retriever alone in treatment of acute stroke due to proximal arterial occlusion. The primary endpoint is the rate of perfect reperfusion score ate the end of the endovascular procedure.
Secondary objectives	To demonstrate that the combined approach of contact aspiration and a stent retrievers is clinically superior than using a stent retriever alone Safety/cost-effectiveness analysis in both arms.
Experimental design	This is a multicenter, prospective, randomized, open-label study with blinded evaluation (PROBE design).
Population involved	Patients greater than 18 years of age who have a clinical diagnosis of AIS from a large cerebral vessel occlusion within 8 hours of symptom onset
Inclusion criteria	- Age 18 and older (i.e., candidates must have had their 18th birthday) - Groin puncture undergone within 8 hrs of first symptoms - Neuroimaging demonstrates large vessel proximal occlusion (distal ICA through MCA bifurcation, M1 or M2) - Consenting requirements met according to French laws - With or without intravenous thrombolysis
Exclusion criteria	- Absence of large vessel occlusion on non-invasive imaging - Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory - Suspected pregnancy; if, in a woman is of child-bearing potential, a urine or serum beta HCG test is positive. - Severe contrast medium allergy or absolute contraindication to use of iodinated products. - Clinical history, past imaging or clinical judgment suggests that the intracranial occlusion is chronic.

	- Patient has severe or fatal comorbidities that will likely prevent improvement or follow-up or that will render the procedure unlikely to benefit the patient. - Acute ischemic stroke involving posterior circulation (basilar occlusion) - Angiographic evidence of carotid dissection or tandem cervical occlusion or stenosis requiring treatment. - Pregnant or breast-feeding women - Patient benefiting from a legal protection - Non-membership of a national insurance scheme - Opposition of the patient or (in case of inclusion as a matter of urgency) of the trustworthy person
Devices	Combined use of contact aspiration and stent retriever mechanical thrombectomy for recanalization Stent retriever mechanical thrombectomy alone for recanalisation
Other procedures added by the research	None
Risks added by the research	None
Number of subjects chosen	Based on literature, we expected perfect recanalization of 70% in experimental arm and 55 % in control arm. To detect this difference using a 2-sided test (alpha risk=5%, power=80%), 163 patients per arm would be required. To anticipate 20% of patients with spontaneous recanalization or catheterization failure, 204 patients per am (a total of 408) will be included.
Number of centers	12 centers
Research periods	36 months - Inclusion period : 24 months - Patients' lengh of participation : 12 months
Statistical analysis	Statistical analyses will be independently performed by the Biostatistics Department of University of Lille. All analyses will be conducted according to the intention-to-treat (ITT) principle. For the main objective, the rate of perfect reperfusion score at the end of the endovascular procedure will be compared between the two treatments groups using a mixed logistic regression model adjusted for prognostic variables considered in minimization randomization algorithm with a random center and center*treatment group effects. Adjusted odds ratio (OR) will be derived from this model as the treatment effect size (experimental vs. control arms).
Clinical event committee	Yes

2 Introduction

2.1 Rationale for study

The treatments for patients with acute ischemic stroke include intravenous (IV) fibrinolysis within 4.5 h since 2008 and endovascular interventions by mechanical thrombectomy up to 6 hours since 2015[1-4].

A meta-analysis – using individual patient data from five randomized controlled trials published in 2014-2015[5-11] – found that endovascular thrombectomy reduced disability at 90 days compared with standard medical treatment (modified Rankin Scale [mRS] score 0–2: 46% vs 27%; P < 0.0001) among patients with acute ischemic stroke caused by occlusion of the proximal anterior artery circulation [12].

Mechanical Thrombectomy Strategy:

Recanalisation rate is a major issue given that favorable clinical outcome after AIS is strongly correlated with successful recanalization[13]. The addition of endovascular thrombectomy to standard medical care also resulted in better 24-hour reperfusion rates (71% of successful recanalization rate TICI2B/3)[14]. In these 5 randomized controlled trials, mechanical thrombectomy was performed in more than 80% of cases with **a stent retriever (SR)**, a self-expanding stent used to retrieve thrombi[11]. The European and American recommendations propose conducting clinical trial to determine the best thrombectomy device and thus increase the recanalization rate.[1-4]

A novel thrombectomy technique – "a direct aspiration first pass technique" (**ADAPT or contact aspiration technique**) – involves the first-line use of aspiration through a large-bore catheter.[15-28]

Contact aspiration is an approach that utilizes the advantages of large bore aspiration catheters that can be easily tracked and introduced into the cerebral circulation to directly remove the thrombus via negative pressure aspiration. If this application is not directly effective, it maintains the thrombus engaged in the catheter tip through suction and the clot is removed as the catheter is pulled out of the body. In the minority of cases where the application of aspiration is not successful in removing the blockage, then the large aspiration catheter provides access to navigate a stent retriever to the location of the thrombus (versatile technique).

Various studies have reported revascularization rates of 65–78% with contact aspiration alone [16, 17, 25, 29, 30]; rising to 82–100% for contact aspiration followed by further endovascular treatment (e.g. stent retriever) [16, 17, 21, 25, 27-30]. Ninety-day mRS 0–2 scores have been reported for 40–56% of patients treated with contact aspiration (with or without further treatment) [16, 21, 25, 27-31]. Four studies[21, 27, 30, 31] – all retrospective – have compared contact aspiration and stent retrievers as first-line endovascular treatment (Table 1). Two have reported significantly improved revascularization rates with contact aspiration [21, 30], two have reported significantly reduced times to revascularization [27, 30], and one has reported significant improvements in clinical outcomes [31].

Initial experience with this approach has shown promising results; however, randomized or direct comparison studies have not been performed. [16, 17]

The concomitant use of contact aspiration technique during stent retriever mechanical thrombectomy (combination of contact aspiration and SR techniques) has been described in retrospective case series.[19, 22, 23, 26]
The advantages of the combined stent-aspiration technique include a flexible large-bore catheter in a triaxial technique, which provides stability for the stent-retriever; and the potential synergistic effect of the techniques of contact aspiration and stent retrieval used simultaneously.
Clinical experience has shown the combination of contact aspiration, and stent retriever techniques to provide rapid, effective, and safe recanalization. [19, 22, 23, 26]

The contact aspiration is clearly a promising treatment, but its potential benefits over stent retrieval have yet to be shown in a prospective randomized trial. ASTER1 is an ongoing randomized clinical trial which aimed to compare use of the contact aspiration technique versus the stent retriever technique in first line. It is an exploratory trial with a radiological endpoint (surrogate marker) defined as the percentage of successful recanalization at the end of the angiogram. ClinicalTrials.gov NCT02523261.

In terms of health costs, cardiovascular diseases account for 10% of total expenditures of Medicare, more than half concerns of two pathologies, acute or chronic coronary disease (4.4 billion) and strokes (3.7 billion) (ONDAM 2011).[32] Ischemic stroke, 130 000 cases per year in France, 1 case every 4 minutes, is the leading cause of acquired disability in adults and the second leading cause of mortality (about 10% of deaths). There are however few medico-economic evaluation studies comparing the effectiveness of mechanical thrombectomy strategies in the treatment of cerebral infarction. French health authority, neurovascular society (Société Francaise de Neurovasculaire - SFNV and Société Francaise de Neuroradiologie - SFNR) are in urgent need of economic data on these acts of thrombectomy procedures (3000-4000 procedures per year in France) already widely performed in France but its reimbursement is under evaluation. A retrospective study suggests that the contact aspiration strategy showed lower device cost versus stent retriever as a first line therapy approaches.[29, 30]

3 Hypothesis

The main hypothesis is that contact aspiration combined with the use of a stent retriever compared to use of a stent retriever alone is superior in the treatment of acute stroke due to proximal arterial occlusion in anterior circulation ischemic strokes by increasing the perfect reperfusion rate.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary Objective:

To show the efficacy of combined use of aspiration and the stent retriever technique compared to the stent retriever alone to improve the perfect reperfusion rate at end of procedure in patients with acute stroke due to proximal arterial occlusion

4.1.2 Secondary Objectives:

- To assess the efficacy of the combined approach of contact aspiration and a stent retrievers compared to the use of stent retriever alone to improve:
  - clinical efficacy outcomes
  - angiographic efficacy outcomes after the frontline strategy and at end of procedure
- To compare the safety of the contact aspiration combined with the use of a stent retriever versus a stent retriever alone.
- To perform a cost effectiveness analysis.

4.1.3 Primary endpoint

Perfect reperfusion rate at the end of angiography defined as a TICI 2c/3 score (TICI score = Thrombolysis In Cerebral Infarction).
The assessment of final revascularization will be conducted by an independent central core imaging laboratory unaware of the study group assignments (blinding endpoint assessment, PROBE DESIGN).

4.1.4 Secondary endpoints

Angiographic efficacy outcomes:

- Rate of successful reperfusion (mTICI 2b/2c/3), and complete reperfusion (mTICI3) at end of endovascular procedure
- Rate of perfect (mTICI 2c/3), successful reperfusion (mTICI 2b/2c/3), and complete reperfusion (mTICI3) after the frontline strategy
- Time from groin puncture to achieve TICI 2c or better revascularization
- Time between groin puncture to clot contact and clot contact to maximum reperfusion

Clinical efficacy outcomes:

- Global disability assessed by overall distribution of modified Rankin scale (mRs) at 90-days and at one year (shift analysis combining scores 5 and 6)
- Rate of favorable functional independence defined as a mRS 0-2 at 90 days and at one year.
- Rate of excellent functional outcome defined as a mRS 0-1 at 90 days and at one year.
- Change in NIHSS from baseline to 24 hours (delta NIHSS)

Safety

- Rate of symptomatic and asymptomatic intracerebral hemorrhage at MRI 24h after thrombectomy (according ECASS3 classification) (independent core lab adjudication).
- Rate of parenchymal hematoma 2
- Rate of all-cause mortality at 90 days and at one year
- Rate of periprocedural complications: Occurrence of emboli to new territory (ENT), vasospasm, dissection, or perforation.
- Rate of procedure-related adverse events.

Cost effectiveness analysis:

- Two points of view will be adopted, the hospital's point of view and that of Medicare.
- The average cost per patient with complete recanalization
- A budget impact analysis (BIA) to assess the economic and financial consequences of the introduction of the combined use of contact aspiration and the stent retriever technique versus stent retriever alone. This will be conducted in accordance with AIB HAS recommendations and will incorporate a study comparing the costs to the rates.
- We estimated the average cost of a gain in autonomy for each patient and / or the average cost of a loss of autonomy for each patient at three months. QALY will be assessed at 3 and 12 month.

4.2 Risk Analysis

The contact aspiration, stent retriever and the contact aspiration and stent retriever combined are already used in a routine practice by all participating centers; however, no randomized studies comparing these 2 strategies have not been performed.
The patients' participation in this study does not add additional risk relative to their usual care.

All information concerning subjects will be kept confidential so as to reduce the risk of a breach of privacy. Subjects will be assigned a study ID #. No personal identifying information will be used in presentation or publication of data from this study.

5 Study population

5.1 Recruitment

The target population for the study is composed of patients greater than 18 years of age who have a clinical diagnosis of AIS from a large cerebral vessel occlusion within 8 hours of symptom onset.
The study team at each site will obtain consent, will determine eligibility and will identify potential study participants and/or their authorized surrogate.

5.2 Inclusion criteria

- Age 18 and older (i.e., candidates must have had their 18th birthday)
- Groin puncture carried out within 8 hours of first symptoms
- Neuroimaging demonstrates large vessel proximal occlusion (distal ICA through MCA bifurcation, M1 or M2)
- Consenting requirements met according to French laws.
- With or without intravenous thrombolysis

5.3 Exclusion criteria

- Absence of large vessel occlusion on non-invasive imaging
- Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory

- Suspected pregnancy; if, a woman is of childbearing potential, a urine or serum beta HCG test is positive.
- Severe contrast medium allergy or absolute contraindication to iodinated agents.
- Patient has severe or fatal comorbidities that will likely prevent improvement or follow-up or that will render the procedure unlikely to benefit the patient.
- Acute ischemic stroke involving posterior circulation (vertebrobasilar occlusion)
- Angiographic evidence of carotid dissection or tandem cervical occlusion or stenosis requiring treatment.
- Patients benefiting from a legal protection
- Non-membership of a national insurance scheme
- Opposition of the patient or (in case of inclusion as a matter of urgency) of the trustworthy person

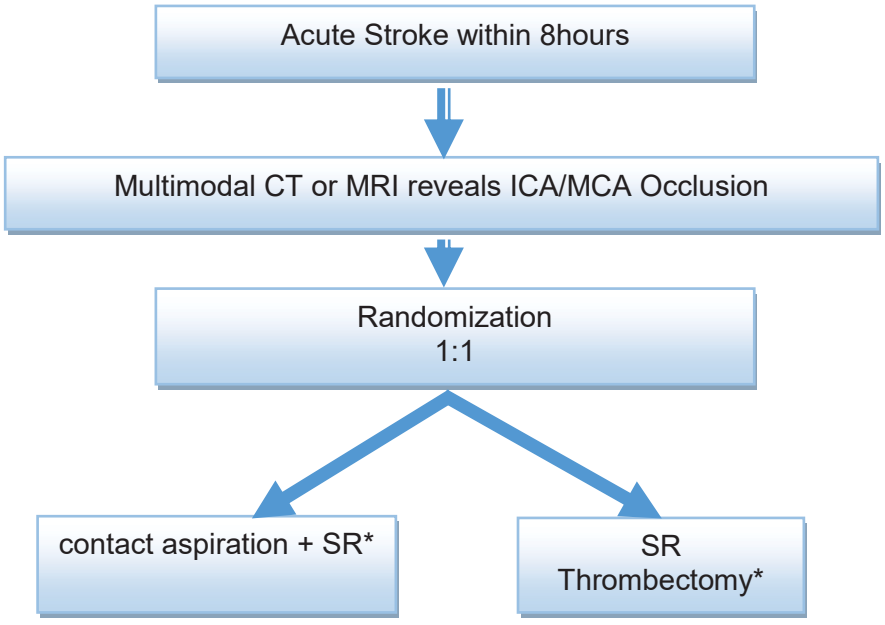
5.4 Expected length of participation and description of the chronology and duration of the research

- Recruitment period: 24 months
- The included subjects' length of participation: 12 months
- Total research period : 36 months

6 Trial design

This is a pragmatic, multicenter, prospective, randomized, open-label study with blinded evaluation (PROBE design). Subjects will be equally allocated (1:1) to endovascular intervention with combined contact aspiration plus stent retriever vs. stent retriever alone.

6.1 Overview of Study Flow



*A balloon guide catheter will be mandatory in both arms.

All sites will keep a screen failure log of all acute stroke patients treated with IAT but who are not randomized into the study. Reason(s) for exclusion will be recorded. Logs will be data entered by the clinical sites on a monthly basis. Recruitment rates will be tracked over time for each hospital. The actual recruitment rates as well as potential recruitment rates will be useful for planning further clinical trials and determining the widespread impact of the therapy.

6.2 Study schedule

Activity	**Baseline**	**Randomization / Procedure**	**24 hrs Post-Randomization**	**90 days Post-Randomization**	**12 months Post-Randomization**
Evaluation of Criteria					
Informed Consent	X				
Randomization		X			
Past Medical History	X				
Clinical Evaluation	X		X	X	
Modified Rankin Scale	X			X[1]	X[1]
NIH Stroke Scale	X		X		
CT/CTA or MRI/MRA[2]	X		X		
Angiogram, TICI scores		X			
Mechanical Thrombectomy Procedure[3]		X			
Concomitant Medications	X	X	X	X	
Adverse Event assessment		X	X	X	X
EuroQol EQ-5D-3L				X	X

[1]*Must be completed by a BLINDED stroke study team member. If possible, it is preferable that these assessments to be completed by a blinded team member at the other time point also.*
[2]*CT/CTA or MRI/MRA are required at baseline and 24hrs post-randomization, and any time there is a neurological deterioration (a change in NIHSS of 4 points or more) or hemorrhage.*
[3]*Must be analyzed by a blinded central imaging core lab.*

All procedures (described above) are carried out routinely as part of the standard care of patients (none is specifically added by the protocol)

6.3 Conduct of the study

6.3.1 Informed Consent

After checking patient eligibility criteria, the main investigator or one of his collaborators (appearing on the function delegation form) will explain to the patient the objectives and the

progress of the study, orally and by means of a written informed consent form (ICF). The ICF should be signed and personally dated by the subject or the trustworthy person and by the person who obtained the consent

Most of the patients eligible for this research will not be in a state of consciousness allowing them to provide this information; furthermore, study inclusion will most often be made in an emergency context. If the state of consciousness of the patient does not allow consent to be obtained, and because of this therapeutic urgency, the consent of a trustworthy person, if he/she is present, will be looked for, without causing delay in the management of the patient. Should this not be possible, the doctor will include the patient according to the protocol of inclusion in an emergency situation When the patient has regained a sufficient state of consciousness, his/her consent to the pursuit of the research and to the treatment of the collected information will be asked for. The patient can drop out of the study at any time on simple demand.

6.3.2 Baseline Evaluation

Once the patient meets all eligibility criteria, and the patient or surrogate has provided written informed consent, he/she will undergo standard non-study surgical preoperative workup including but not limited to: demographic confirmation, medical history, and focused physical examination. Baseline imaging may either be CT/CTA or MRI/MRA with or without perfusion prior to the pre-procedure angiography (cf 6.3.3). The baseline neurologic examination will be performed by a health care provider or study team member, certified to administer the exam and able to give an unbiased neurological and functional assessment (pre-stroke mRS and presentation NIHSS). A pregnancy test will be conducted for all applicable subjects (females <50 years old and of child bearing potential).

6.3.3 Imaging Assessment for Eligibility for Trial Participation

The subject should be clinically evaluated in the same manner as any routine acute ischemic stroke patient. Clinical assessment documenting NIHSS and significant past medical history should be obtained. Imaging with CT or MR, performed as per the institutional standard of care, is required to exclude acute intracranial hemorrhage. Additional anatomic and/or physiologic imaging with CT or MR perfusion imaging, again performed according to the institutional standard of care, should then be performed on patients that have no evidence of significant ischemia on initial scans. Anatomic imaging can utilize CT angiography (CTA) with contrast bolus imaging to visualize the vessels of the head as well as presence of collateral circulation. Similar anatomic cerebral imaging can be performed with MR angiography (MRA). The studies must demonstrate an acute major vessel intracranial anterior circulation occlusion (ICA or MCA).

All MRIs will be performed on MR scanners equipped with echo-planar imaging capability to allow rapid acquisition of diffusion and perfusion scans.

Perfusion imaging is not required for this trial.

6.3.4 Randomization

Immediately after baseline brain imaging and prior to endovascular procedure, patients will be randomly allocated in a one-to-one ratio to receive either the combined contact aspiration combined with Stent retriever approach (experimental arm) or the stent retriever alone approach (control arm).
To assure a centralized real time randomization procedure, a web-based randomization will be performed using the electronic case-report form (eCRF) system.The patient randomization numbers will be allocated sequentially in the order in which the patients are randomized. A dynamic randomization procedure by minimization will be done for achieving a balance of the following factors related to final mTICI or endovascular procedure : age (70≤ vs. >70), prior use of IV thrombolysis, occlusion site (isolated middle cerebral artery versus middle cerebral artery/internal carotid artery). The center will be also considered in the minimization method. Patients are enrolled and randomized by vascular neurologists and interventional neuroradiologists.

6.3.5 Procedures

Pre-Procedure Angiography (standard care)

If the patient is randomized to mechanical thrombectomy, the groin puncture to initiate the procedure should occur within 1 hour of the clinical imaging used to determine trial candidacy. An introducer sheath will be placed in the femoral artery. Diagnostic angiography is initially performed via the transfemoral approach with catheterization of the carotid artery appropriate to the patient's presenting symptoms. Once thrombus in the appropriate vessel is identified, the thrombectomy procedure will be initiated.

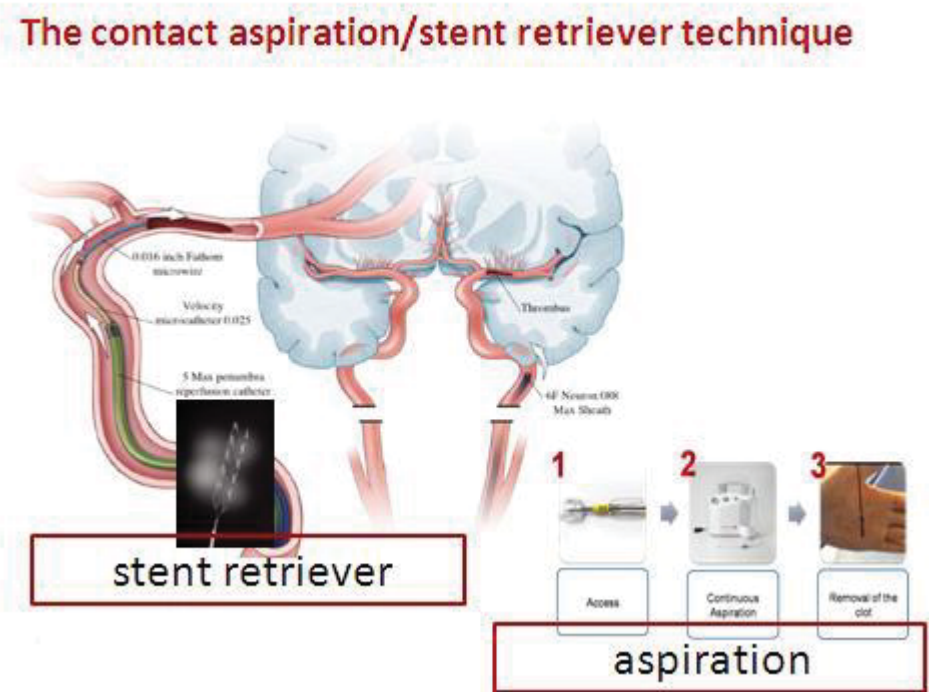
As per local standard of care and prior to the thrombectomy, a Digital Subtraction Angiography (DSA) will be performed to define the angiographic architecture of the occluded vascular segment. When possible, an assessment of collateral blood flow by DSA should be made as per the institutional standard of care, particularly in cases of terminal internal carotid artery occlusion. Prior to mechanical thrombectomy by the thrombectomy device, baseline Thrombolysis in Myocardial Infarction/Thrombolysis in Cerebral Infarction (mTICI) and Artery Occlusion Lesion (AOL) scores by DSA (see annexes) will be obtained.

Combined contact aspiration/Stent Rtriever Technique [22, 23, 31] :

The combined contact aspiration/SR approach is performed, as in standard care, using a long sheath positioned in the distal cervical vasculature using an exchange technique. A 0.021 to 0.027 inch inner lumen microcatheter with a 0.014 to 0.016 inch microwire inside is then introduced into a large-bore aspiration catheter and this construct is introduced into the long sheath as a unit.
A large bore balloon guide catheter as to be placed into the cervical ICA. The microcatheter is then advanced past the thrombus over the microwire and the large-bore aspiration catheter is advanced as close to the proximal aspect of the thrombus as possible prior to stent-retriever deployment. Any CE-marked stent retriever device is then deployed across the occlusion. A control superselective

angiogram may be used to document the extent of occlusion and thrombus. The stent-retriever is then deployed across the thrombus via the microcatheter and the microcatheter subsequently removed completely from the patient. After a 3 min waiting period, the large-bore aspiration catheter is connected to a continuous aspiration from the dedicated aspiration pump and tension is applied on the stent-retriever delivery wire to pull it into the aspiration catheter while simultaneously advancing the aspiration catheter up to the face of the thrombus and past the origin of the anterior cerebral artery. If the thrombus becomes lodged between the stent-retriever and the tip of the aspiration catheter, then the system will carefully removed as a unit under continuous aspiration while also manually aspirating through the long sheath positioned in the cervical vasculature.

This process is repeated until successful reperfusion (Thrombolysis In Cerebral Infarction (TICI) 2b/3) is achieved or the procedure terminated. At least 3 attempts must be made before changing to use of other adjunctive devices. A revascularization score will be recorded after each device attempt.



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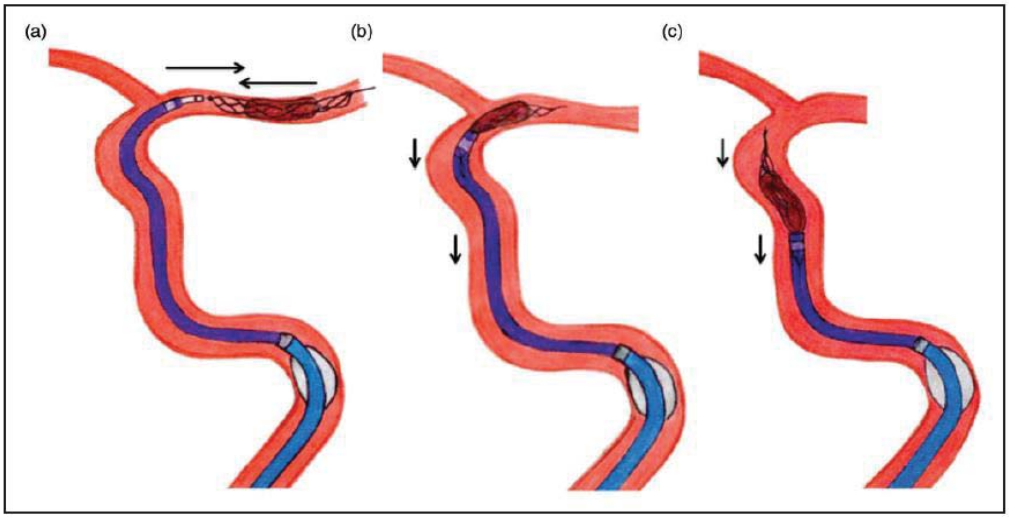


Figure 2. Illustration of the Aspiration–Retriever Technique for Stroke in a middle cerebral artery M1 occlusion. (a) The Max ACE aspiration catheter is navigated into the patent segment of the middle cerebral artery to face the thrombus. A stent retriever device is placed across the thrombus and allowed to intercalate within the clot. Before activating the Penumbra aspiration pump apparatus the balloon guiding catheter, if used, is inflated. (b), (c) When resistance is felt while retracting the stent retriever, the entire assembly (5 Max ACE aspiration catheter and the partially resheathed stent retriever) is locked and slowly withdrawn under continuous aspiration with additional flow arrest.

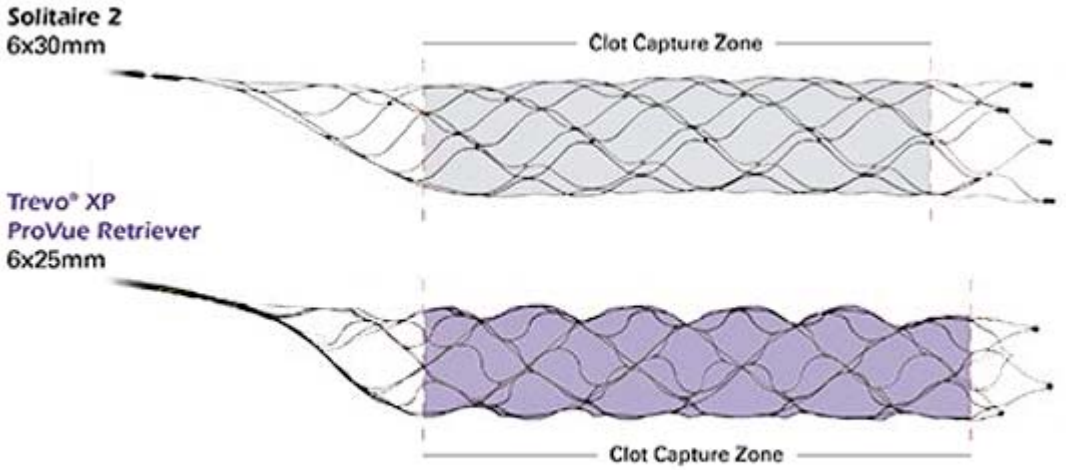
Stent retriever technique[11] :

The technique used should be in accordance with the device IFU. A large bore balloon guide catheter as to be placed into the cervical ICA.

If a balloon guide catheter cannot navigate or be deemed suitable for the treating vessel, then the largest bore access guide catheter possible is recommended. If local aspiration in conjunction with the stent retriever is preferred by the operator, then the largest caliber aspiration catheter should be placed as close to the proximal clot as possible. A suitable delivery microcatheter is navigated over a microwire into the occluded MCA and across the occlusion.

A suitable delivery microcatheter is navigated over a microwire into the occluded MCA and across the occlusion. A control superselective angiogram may be used to document the extent of occlusion and thrombus. Any CE-marked stent retriever device is then deployed across the occlusion.

A minimum of 3 attempts with SR should be performed. A revascularization score will be recorded after each device attempt.



Stent retriever device: The example of the SOLITAIRE™ or TREVO flow restoration system.

Immediate post-treatment angiograms

Immediate post-treatment angiograms in the anterior/posterior, lateral, and working positions will be obtained, and de-identified DICOM images will be submitted to the Independent Core Lab (ICL). The site Investigator will take necessary steps to ensure that pre- and post- placement angiograms are performed using similar views, magnifications, and contrast amount so as to ensure valid "before-after" comparisons. mTICI scores are to be assessed after completion of the procedure. Note should be made of any complicating factors such as vessel dissection or perforation. Pre-procedure and post-procedure angiograms shall be sent to an independent Core Laboratory (who is blinded to treatment assignment and clinical status) to make a final determination on mTICI flow.

Modified Thrombolysis In Cerebral Infarction scale (TICI) scale including a 2C designation [15]

Score	**Revised TICI**
0	No perfusion or anterograde flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
2A	Some perfusion with distal branch filling of <50% of territory visualized
2B	Substantial perfusion with distal branch filling of ≥50% of territory visualized
2C	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

6.3.6 Post-Procedure Care

Standardization of post procedure medical management in both arms will occur according to the European guidelines.[1, 2]

Neurological and functional exams will be conducted (NIHSS and mRS at a minimum) within 24 (+/-12) hours of randomization by a dedicated, pre-specified Blinded Study Stroke team member with NIHSS and mRs certifications.

Follow-up imaging (i.e., non-contrast CT scan or MRI) will be performed at 24 (+/-12) hours after randomization, and will be reviewed to assess hemorrhagic transformation Hyperintense or hypersignal regions consistent with acute hemorrhage will be identified by visual inspection on the noncontrast CT or GRE sequences and outlined by hand to provide lesion volumes. Regions of hemorrhagic transformation will be categorized as petechial hemorrhage or hematoma according to the ECASS III classification scheme:

HI 1:	Small petechiae along the margins of the infarcted area without space-occupying effect
HI 2:	More confluent petechiae within the infarcted area but without space-occupying effect

PH 1:	Hematoma in <30% of the infarcted area with some slight space occupying effect
PH 2:	Hematoma in >30% of infarcted area with substantial space occupying effect
IVH	Intraventricular Hemorrhage
RH	Remote Hemorrhage, defined as hemorrhage in brain areas remote from infarcted tissue
SAH	Subarachnoid hemorrhage

In addition, any neurological deterioration should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice.
A symptomatic intracranial hemorrhage will be defined as 24-hour CT evidence of an ECASS defined intracerebral and a 4-point or more worsening of the NIHSS score.

6.3.7 Recovery and Discharge

The subject will be recovered from the treatment and discharged from the hospital in accordance with standard practices.

6.3.8 Follow-Up Examination (90 days post-randomization)

Two clinical outcome measures were selected for this study. These were chosen on the basis of their

reliability, familiarity to the neurologic community, contact aspiration ability for use in patients who have had a stroke, and comparability to end points used in other trials of thrombolytic therapy. The modified Rankin Scale (mRS) is an overall assessment of global handicap. In the original Rankin Scale, a score of zero indicates the absence of symptoms and a score of 5, severe disability. The modified Rankin Scale adds a score of 6 for fatal outcomes. The National Institutes of Health Stroke Scale (NIHSS) is a 42 point scale that quantifies neurologic deficits in 11 categories. Normal function without neurologic deficit is given a score of zero.

The 24hr Post-Randomization (NIHSS) and Day 90 (mRS) clinical outcome measures will be assessed by a dedicated, pre-specified Blinded Study Stroke team member with NIHSS/mRs certifications. The modified Rankin Scale score at 90 days will be assessed by trained research nurses unaware of the study group assignments, during face-to-face interviews or via telephone conversations.

6.3.9 Follow-Up Examination (12 months post-randomization)

Twelve months after the randomization, the overall assessment of global handicap (mRS) and the quality of life (EuroQol EQ-5D-3L) will be assessed by trained research nurses unaware of the study group assignments, during face-to-face interviews or via telephone conversations.

6.4 Medication during Treatment

Subjects will undergo the index study treatment procedure as per the standard anesthetic protocol at the individual clinical site. Concomitant medications and therapies will be administered using standard hospital practice. Administration and dosage of these medications will be noted in the study CRF.
No concomitant medication is prohibited.

7 Devices

All devices required to perform the procedure are to be provided by the site and are available commercially for the indications for which they are proposed in this study.

Devices that may be used during the Thrombectomy Procedure:

Access devices:	Guiding catheter and sheath
Thrombectomy devices:	All CE-marked cerebral aspiration catheters and stent retriever thrombectomy devices are allowed.

	Aspiration catheter should be plugged to a dedicated aspiration pump
Non-ionic contrast:	Institutional standard of care
Guidewires:	Investigator preference from CE-cleared devices and standard of care
Additional:	Any other adjunctive, approved/cleared device for IA stroke treatment

8 Hospital Costs

Cost effectiveness analysis: QALY assessment

- Micro costing: For each subject, device costs (the market price for all devices used) will be collected for the hospitalization during which the index procedure took place. These costs will include device costs, materials used to treat the occlusion, and number of days spent in the hospital (ICU and non-ICU length of stay).
- MRS and EQ-5D-3L at 3-month
- MRS and EQ-5D-3L at 12-month

9 Statistical Evaluation

9.1 Sample Size Estimation for the Primary Outcome

The objective is to show the superiority for perfect recanalization (TICI2c/3) of thrombectomy using combined aspiration+SR strategy as first-line treatment (experimental) compared to first-line "stent retriever devices" (control). Based on literature, we expected perfect recanalization of 70% in experimental arm and 55% in control arm, corresponding to an absolute and relative increase in favor of experiment arm of 15% and 27%, respectively. To detect this effect size using a 2-sided test (alpha risk=5%, power=80%), 163 patients per arm would be required. To anticipate 20% of patients with spontaneous recanalization or catheterization failure, we planned to include 204 patients per am (a total of 408) .

9.2 Method and analysis Strategy

Statistical analyses will be independently performed by the Biostatistics Department of University of Lille under the responsibility of Professor Alain Duhamel. For data analysis, statisticians and investigators will be aware of the treatment group allocation. Data will be analyzed using the SAS software (SAS Institute Inc, Cary, NC, USA) and all statistical tests will be performed with a 2-tailed alpha risk of 0.05. A detailed statistical analysis plan will be written and finalized prior to the database lock. Baseline characteristics will be described for each arm and absolute standardized differences will be calculated. Quantitative variables will be expressed as mean (standard deviation)

or median (interquartile range) for non-Gaussian distribution. Qualitative variables will be expressed as frequencies and percentages. Normality of distribution will be assessed graphically and using the Shapiro-Wilk test. All analyses will be performed in all randomized patients based on their original group of randomization, according to the intention-to-treat principle. The final report will be written, based on the CONSORT statement recommendations.

9.3 Main Objective:

The rate of perfect reperfusion at the end of the endovascular procedure will be calculated and compared between the two treatment groups using a mixed logistic regression model adjusted for prognostic variables considered in minimization randomization algorithm (prior use of intravenous thrombolysis, occlusion site (age (70≤ vs. >70), baseline ASPECT score (0-5 vs. 6-8 vs. 9-10), prior use of IV thrombolysis, admission NIHSS (17< vs. ≥17), occlusion site (isolated middle cerebral artery versus middle cerebral artery/internal carotid artery)) with a random center and center*treatment groups effects. Adjusted odds ratio (OR) will be derived from this model as the treatment effect size (experimental relative to control strategy). Using the method described by Austin[36], absolute and relative risk differences will be derived from the marginal probabilities of perfect reperfusion.

As exploratory analyses, heterogeneity in treatment effect size on primary outcome across key subgroups will be evaluated by including the corresponding multiplicative interaction terms in the multivariate mixed logistic regression models. From these models, treatment effect sizes (adjusted OR) will be estimated in each subgroup. The following key subgroups will be investigated:

- Age (≤70 vs. >70 years)
- Time from onset to randomization (≤ 300 vs. > 300 minutes)
- Baseline site of thrombi on vascular imaging (isolated MCA vs. ICA/tandem MCA, as adjudicated by the core lab)
- Prior use of IV alteplase (yes vs. no)
- Clot Burden score (<6 vs. ≥6)
- Collateral status (good versus poor, as adjudicated by the core lab on initial angiogram)
- Morphology of the occlusion (regular or irregular clot)

Secondary Objectives:

Secondary binary outcomes will be also analyzed using a mixed logistic regression model including the same fixed and random effects; adjusted ORs will be calculated as the treatment effect size. For procedure-related serious adverse events, only the rate of patients with at least one adverse event will be compared between the two groups (based on subject counts and not on event counts). The rate of specific adverse events will be evaluated descriptively. The secondary ordinal outcome (distribution of 90-day and 1-year mRS, after combining scores of 5 and 6) will be analyzed using a mixed ordinal logistic regression model including the same fixed and random effects that previous

models; adjusted common OR will be calculated as the treatment effect size. The change in NIHSS score at 24h will be analyzed using the constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger[37] including the same fixed and previous models. This model will be used in view of the potential advantages of the cLDA compared to the conventional longitudinal analysis of covariance (ANCOVA) model[38]. In the cLDA, both the baseline and post-baseline values are modeled as dependent variables using a linear mixed model (using an unstructured covariance pattern model), and the true baseline means are constrained to be the same for the 2 treatment groups. Hence, the cLDA provides an adjustment for the observed baseline difference in estimating the treatment effects, using all available baseline and post-baseline values. The between-group mean differences in 24-hour change in NIHSS will be estimated by the time-by-arm interaction as treatment effect size. If normality of model residuals are not satisfied, nonparametric analysis will be used; absolute changes between baseline and 24 hours will be calculated and compared between the 2 treatments groups using non-parametric analysis of covariance adjusted for baseline values[39]. The others secondary quantitative outcomes (the reperfusion times) will be analyzed using a mixed linear regression model including the same fixed and random effects that previous models; the between-group mean differences in time will be derived from model as effect size. In normality of model residuals are not satisfied (even after a logarithmic transformation), nonparametric analysis will be used; quantitative outcome will be compared using the Mann-Whitney U test. All secondary objectives will be considered as exploratory and no correction for multiple comparisons will be applied.

9.4 Missing Data and Imputation Methods

Under the ITT principle, all patients who are randomized are included in the analysis.

Since we expected no missing data on primary outcome (assessed immediately after endovascular procedure), no imputation procedure will be applied. In cases of catheterization failure, primary outcome will be considered as perfect reperfusion whatever the treatment group. In cases of spontaneous complete recanalization before endovascular treatment primary outcome will be considered as perfect reperfusion whatever the treatment group. In case of missing core laboratory reading (whatever the reason), the study site evaluation of mTICI grade will be used to handle missing value in primary outcome.
For other secondary outcomes no imputation procedure will be used, except for core laboratory outcomes where missing values were replaced study site evaluation. Every effort is to be made to keep all missing data, particularly the Day 90 outcomes, to a minimum. The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal.

9.5 Blinding

Regarding the primary end-point, first, a central invasive imaging core lab, not involved in the trial patient management, will record the mTICI score, collaterality status, and periprocedural

complications. In cases of disagreement between the two assessors, a centralized neurointerventionalist will review angiograms and decide on the primary end-point value. All neuroimaging secondary end-points (in CT or MR images) including sites of arterial occlusion, clot burden score, recanalization at 24 hours, infarct volume and hemorrhage, will be determined by the CT/MR non-invasive imaging core-lab, which also will be blinded to treatment allocation. The modified Rankin Scale score at 90 days will be assessed by trained research nurses unaware of the study group assignments, during face-to-face interviews or via telephone conversations.

9.6 Subject Discontinuing Rules

9.6.1 Study Withdrawal

Subjects may be withdrawn from the study for the following reasons:

- Voluntary withdrawal of consent — meaning that a subject voluntarily chooses not to participate further in the study. In case of withdrawal of consent, the data already obtained concerning the subject will be used unless it states in writing that it opposes their use. Stopping participation of a subject will not change the routine patient management.
- Subjects may also be withdrawn at the investigator's discretion if it is considered to be in their best interest.

The sponsor can early stop all or part of the study, temporarily or permanently. For example:

- if new information relating to the experimental medical device leading to reassess the benefit-risk ratio for the study ;
- if inclusion targets are unmet.

9.6.2 Unattended Visits

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). If the missed visit was due to a serious adverse event, (e.g., re-hospitalization) an Adverse Event report must be completed in the study database and any reporting requirements met.

10 Safety

As part of research to assess standard care, acts or medical strategies are part of the routine practice and are used in accordance with their instructions.
The potential adverse events are those related to the patient's usual care and do not require a specific statement by the sponsor.
Adverse events and procedure-related complications will be adjudicated by the event committee that will be blinded to the treatment arm

11 Data Collection

11.1 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system entitled “captur system” that provides a user-friendly and easy-to-navigate interface.

Data will be recorded in an electronic case report forms (eCRF), developed using Clinsight (ENNOV). The eCRF will be subjected to data entry at each investigator site and every center will be responsible of the patient’s anonymization. The eCRF will be created, tested and validated before the start of data capture. The essential data necessary for monitoring the primary and secondary endpoints will be identified and managed at regular intervals throughout the trial. Data will be monitored by the data management team of the data-management department of University Hospital of Lille by using the predefined rules and queries will be automatically edited. Finally, an overall automated monitoring will be done by the data manager at the end of the data entry. In case of discrepancies, queries will be edited to resolve the problems encountered.

11.2 Randomization Module

The web-based Randomization Module will be used by authorized site personnel for the purpose of randomizing eligible patients. The Study Coordinator (or other appropriate study team member) will log onto the eCRF using a unique username and confidential password. When a subject is deemed eligible, a unique subject ID and record will be generated in “captur system”. Once the Study Coordinator has entered the required subject information and clicked “Randomize,” the computer program will display the treatment assignment for the subject. The subject is considered randomized and enrolled at the time the eCRF generates the treatment assignment.

12 Administrative And Regulatory Considerations

12.1 Permissions to access data and source documents

The medical data for each patient will only be sent to the sponsor or persons authorized by the sponsor and to competent health authorities (if applicable), subject to terms guaranteeing their confidentiality.

The sponsor and the regulatory authorities may request direct access to medical records for the purposes of verification of the procedures and/or data of the study, without breaching their confidentiality and to the extent permitted by applicable laws and regulations.

Data collected during the study will be processed electronically in compliance with the requirements of the CNIL (compliance with the French Reference Methodology MR003).

12.2 Monitoring

Monitoring visits will be scheduled regularly by a Clinical Research Assistant (CRA)

During these visits, the CRA will review study plan compliance, adherence to the protocol, and data quality. The CRA will compare CRFs and ensure that the study is being conducted in compliance with pertinent regulatory requirements.
The protocol has been classified according to the estimated level of subject risk: Predictable risk similar to that of standard care

The investigator will provide the CRA with direct access to CRFs and to the subject's records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification, as well as to any other study documents.

12.3 Ethical Considerations

12.3.1 Written informed consent form

The investigator agrees to provide the subject with clear and precise information about the protocol and request him/her for written informed consent (information form and consent form appended). The investigator will give the subject a copy of the information form and consent form. The subject can only be enrolled in the study after reading the information form and signing and dating the consent form. If this is not possible, a third party (independent from the study) proves the subject's consent. The investigator should also sign and date the consent form. Both documents should be issued at least in duplicate hard copy format so that the patient and the investigator can each keep a copy. The investigator's original will be placed in the investigator's file.

12.3.2 Ethical Review Board

The sponsor agrees to submit the study to an Ethical Review Board (CPP IDF VII) for prior approval.

12.3.3 Modifications to the protocol

Requests for substantial modifications should be addressed by the sponsor for approval or notification to the Ethical Review Board.
The amended protocol should be a dated updated version. If necessary, the information form and consent form should be amended.

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14 Annexes

14.1 Classification mTICI (modified Thrombolysis in Cerebral Infarction)

Score	Revised TICI
0	No perfusion or anterograde flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
2A	Some perfusion with distal branch filling of <50% of territory visualized
2B	Substantial perfusion with distal branch filling of ≥50% of territory visualized
2C	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

14.2 Arterial occlusive lesion - AOL score

Score	AOL Recanalization
0	No recanalization of the primary occlusive lesion
I	Incomplete or partial recanalization of the primary occlusive lesion with no distal flow
II	Incomplete or partial recanalization of the primary occlusive lesion with any distal flow
III	Complete recanalization of the primary occlusion with any distal flow

14.3 Modified Rankin score (mRS)

0	Aucun symptôme	No symptoms.
1	Pas d'incapacité en dehors des symptômes : activités et autonomie conservées	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Handicap faible : incapacité d'assurer les activités habituelles mais autonomie	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Handicap modérée : besoin d'aide mais marche possible sans assistance	Moderate disability. Requires some help, but able to walk unassisted.
4	Handicap modérément sévère : marche et gestes quotidiens impossibles sans aide	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Handicap majeur : alitement permanent, incontinence et soins de nursing permanent	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Décès	Dead.

14.4 NIHSS score : stroke severity assessment

Item	Intitulé	cotation	score	
1a	**vigilance**	**0** vigilance normale, réactions vives 1 trouble léger de la vigilance : obnubilation, éveil plus ou moins adapté aux stimulations environnantes **2** coma ; réactions adaptées aux stimulations nociceptives **3** coma grave : réponse stéréotypée ou aucune réponse motrice		
1b	**orientation** (mois, âge)	**0** deux réponses exactes 1 une seule bonne réponse **2** pas de bonne réponse		
1c	**commandes** (ouverture des yeux, ouverture du poing)	**0** deux ordres effectués 1 un seul ordre effectué **2** aucun ordre effectué		
2	**oculomotricité**	**0** oculomotricité normale 1 ophtalmoplégie partielle ou déviation réductible du regard **2** ophtalmoplégie horizontale complète ou déviation forcée du regard		
3	**champ visuel**	**0** champ visuel normal 1 quadranopsie latérale homonyme ou hémianopsie incomplète ou négligence visuelle unilatérale **2** hémianopsie latérale homonyme franche **3** cécité bilatérale ou coma (1a=3)		
4	**paralysie faciale**	**0** motricité faciale normale 1 asymétrie faciale modérée (paralysie faciale unilatérale incomplète) **2** paralysie faciale unilatérale centrale franche **3** paralysie faciale périphérique ou diplégie faciale		
5	**motricité membre supérieur**	**0** pas de déficit moteur proximal 1 affaissement dans les 10 secondes, mais sans atteindre le plan du lit. **2** effort contre la pesanteur, mais le membre chute dans les 10 secondes sur le plan du lit. **3** pas d'effort contre la pesanteur (le membre chute mais le patient peut réaliser une contraction musculaire avec ou sans mouvement du membre.) **4** absence de mouvement (coter 4 si le patient ne fait aucun mouvement volontaire) **X** cotation impossible (amputation, arthrodèse)	**Dt**	**G**
6	**motricité membre inférieur**	**0** pas de déficit moteur proximal 1 affaissement dans les 5 secondes, mais sans atteindre le plan du lit. **2** effort contre la pesanteur, mais le membre chute dans les 5 secondes sur le plan du lit. **3** pas d'effort contre la pesanteur (le membre chute mais le patient peut faire un mouvement tel qu'une flexion de hanche ou une adduction.) **4** absence de mouvement (le patient ne fait aucun mouvement volontaire) **X** cotation impossible (amputation, arthrodèse)	**Dt**	**G**
7	**ataxie**	**0** ataxie absente 1 ataxie présente pour 1 membre **2** ataxie présente pour 2 membres ou plus		
8	**sensibilité**	**0** sensibilité normale 1 hypoesthésie minime à modérée **2** hypoesthésie sévère ou anesthésie		
9	**langage**	**0** pas d'aphasie 1 aphasie discrète à modérée : communication informative **2** aphasie sévère **3** mutisme ; aphasie totale		
10	**dysarthrie**	**0** normal 1 dysarthrie discrète à modérée **2** dysarthrie sévère **X** cotation impossible		
11	**extinction, négligence**	**0** absence d'extinction et de négligence 1 extinction dans une seule modalité, visuelle ou sensitive, ou négligence partielle auditive, spatiale ou personnelle. **2** négligence sévère ou anosognosie ou extinction portant sur plus d'une modalité sensorielle		
		TOTAL		

Table 1 Studies comparing contact aspiration with stent retrievers (additional procedures allowed in all studies)

	Lapergue et al. [21]	Stapleton et al. [27]	Delgado Almandoz et al. [31]	Turk et al. [30]
Techniques	Contact aspiration vs stent retriever	Contact aspiration vs stent retriever	Contact aspiration vs stent retriever + aspiration	Contact aspiration vs stent retriever + aspiration vs aspiration
Patients	124 vs 119	47 vs 70	45 vs 55	64 vs 30 vs 128
Revascularization rate,* %	82.3 vs 68.9 **P = 0.015**	82.9 vs 71.4 P = 0.19	88.9 vs 83.6 P = 0.6	95.3 vs 83.3 vs 78.6 **P = 0.006**
Time to revascularization,† min	45 vs 50 P = 0.42	294 vs 347 **P < 0.01**	50 vs 51 P = 0.8	37 vs 47 vs 88 **P < 0.0001**
Good clinical outcome (mRS 0–2 at 90 days), %	53.0 vs 54.8 P = 0.97	48.9 vs 41.4 P = 0.45	55.6 vs 30.9 **P = 0.015**	46.7 vs 43.3 vs 36.4 P = 0.40
SICH, %	2.4 vs 5.9 P = 0.21	NR NS	2.2 vs 12.7 P = 0.07	NR
Mean total hospitalization cost, $	NR	NR	NR	33,611 vs 54,700 vs 51,599 **P < 0.0001**

Bold P values are significant.
*mTICI 2b–3 in Lapergue et al. [21]; TICI 2b/3 in the other studies [27, 30, 31].
†Median time from puncture to revascularization.
mTICI, modified Thrombolysis In Cerebral Infarction; mRS, modified Rankin Scale; NR, not reported; SICH, symptomatic intracerebral hemorrhage; TICI, Thrombolysis In Cerebral Infarction.

Liste des centres participants et investigateurs principaux

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