

Contact Aspiration or Stent-Retriever–Assisted Intra-Arterial Lysis for Medium Vessel Occlusions: The SAIL-MeVO Randomized Trial

Thrombectomy in medium vessel occlusions.

Study Protocol Version: Version 2.1

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V2.1 – DATE: 08/Sept/2026

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

INVESTIGATOR AGREEMENT

I have read and understand the SAIL-MeVO Clinical Trial protocol and agree to adhere to the requirements.

I agree to conduct or supervise the research and ensure that copies of the protocol are provided to the study personnel under my supervision and that they are fully informed regarding the investigational plan. I will ensure to conduct the study as described in the protocol and in accordance with relevant parts of the International Conference on Harmonization, Good Clinical Practice (GCP): Consolidated Guideline, the Declaration of Helsinki, EN ISO14155 Clinical Investigations of Medical Devices for Human Subjects, and all applicable local requirements for sites.

I agree to comply with all the requirements and obligations of clinical investigators and/or the laws and regulatory requirements of the country in which the site is located.

I agree to retain adequate and accurate records and to make that those records are made available for inspection in compliance to the study protocol.

I agree to comply with all the laws and regulations governing financial disclosure and to provide up-to-date disclosures, during the study period.

Clinical Site

Site Investigator Signature

Date

Print name

Date

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ABBREVIATIONS

aICV	Automated Non-contrast CT Infarct core volume detection software
AE	Adverse Event
AHA	American Heart Association
ASA	American Stroke Association
AIS	Acute Ischemic Stroke
ASPECTS	Alberta Stroke Program Early CT Score
CCC	Central Coordinating Center
CRF	Case Report Form
CT	Computed Tomography Imaging Scan
CTA	Computed Tomography Angiography Imaging Scan
CTP	Computed Tomography Perfusion Imaging Scan
DSMB	Data and Safety Monitoring Board
DWI	Diffusion Weighted Imaging Scan (Magnetic Resonance Imaging)
e-ASPECTS scores	Automated clinical decision support software for grading ASPECTS
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture System
EQ-5D-5L	Five-level European Quality of Life Score
FDA	U.S. Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IIS	Investigator-Initiated Study

INR	International Normalized Ratio
IQR	Interquartile Range
IRB	Institutional Review Board
IRB/EC	Institutional Review Board/Ethics Committee
IVT	Intravenous Thrombolysis
LKN	Last Known Normal
LVO	Large Vessel Occlusion
MeVO	Medium Vessel Occlusion
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging Scan
mRS	Modified Rankin Scale
mTICI	Modified Treatment in Cerebral Ischemia Scale
NCCT	Non-contrast Head CT Imaging Scan
NIHSS	National Institutes of Health Stroke Scale
PH2	Parenchymal Hematoma Type 2
PI	Principal Investigator
PTT	Partial Thromboplastin Time
RCT	Randomized Controlled Trial
SAC	Statistical Analysis Committee
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAPE	Serious Adverse Procedural Event
sICH	Symptomatic Intracranial Hemorrhage
SSL	Secure Socket Layer
TICI	Treatment in Cerebral Ischemia Scale

TMax Imaging	Time to Maximum of the Tissue Residue Function (Perfusion Parameter)
UADE	Unanticipated Adverse Device Effect

SAIL-MeVO Trial: Endovascular Treatment vs Best Medical Therapy for Medium Vessel Occlusions – Randomized Controlled Trial (V2.1)

2 Synopsis

2.1 Background & Rationale

Distal/medium vessel occlusions (MeVOs: Non dominant M2–M3 MCA, A2–A3 ACA, P2–P3 PCA) represent a substantial proportion of ischemic strokes. While EVT became standard treatment for LVOs, clinical benefit in MeVOs remains uncertain due to vessel caliber and tortuosity. Modern small-caliber aspiration (ADAPT) and stent-retriever–assisted intra-arterial lysis (SAIL) may improve access and microcirculatory perfusion in these territories. This RCT tests whether a pragmatic EVT strategy (ADAPT first, SAIL when anatomy is not favorable) improves functional outcomes versus BMT.

2.2 Funding Sources

Investigator Initiated Study

2.3 Study Devices

CE-approved devices and thrombolytic drugs currently used for mechanical thrombectomy and intra-arterial thrombolysis in stroke.

2.4 Study Aims

Primary Aim: Determine whether EVT improves functional independence at 90 days (mRS 0–2) versus BMT in MeVO stroke patients.

Key hypothesis: EVT yields a 14% absolute increase in mRS 0–2 at 90 days compared with BMT.

Secondary objectives (efficacy only; no recanalization endpoints): (i) ordinal mRS shift at 90d; (ii) excellent outcome mRS 0–1 at 90d; (iii) Dramatic neurological improvement at 24h (Δ NIHSS ≥ 8 or NIHSS ≤ 2); (iv) infarct volume at 24–48h; (v) discharge disposition & length of stay; (vi) EQ-5D-5L at 90d + Domain specific PROMS;

2.5. Study Design

- Type: Prospective, randomized, open-label with blinded endpoint assessment (PROBE). Patients presenting with symptoms of AIS and confirmed MeVO on admission CTA, NIHSS ≥ 9 and ≤ 17 , and within the protocol-defined <12-hour onset/reference-time window will be assigned to receive BMT Vs BMT+EVT

- **Randomization:** 1:1 via secure web-based system; permuted blocks per center; stratified by age (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and IVT use. Randomization stratification factors and center will be included in the primary model.
 - **Sample size (prelim.):** Assuming mRS 0–2 = 43% in the control arm, and 57% ($\Delta=14\%$) in the BMT+EVT arm, $\alpha=0.05$, power=80% $\rightarrow$ **n=200/arm (400 total)**; with 5% attrition $\rightarrow$ **~420 total**.
-

2.6 Interventions

Control (BMT): Guideline-based medical therapy, including IV thrombolysis when indicated.

EVT arm: Stepwise protocol

1. ADAPT – preferred first-line technique when the aspiration catheter can be safely and readily advanced to the target occlusion; a maximum of two aspiration attempts is permitted before transition to SAIL.
2. SAIL – may be used as the initial technique when vascular anatomy is unfavorable for safe distal aspiration-catheter navigation, or as rescue after failure of ADAPT (maximum two aspiration attempts). Permitted pharmacological agents are alteplase, tenecteplase, tirofiban, or eptifibatide (Integrilin), according to protocol dosing, with careful hemodynamic and neurological checks.

Procedural details (catheter models, wire/guide selection, lysis dosing windows, and stop rules) will be specified in the Operations Manual.

Each treated patient will be followed and assessed 3 months after randomization by an independent investigator blinded to allocated arm.

Primary Hypothesis

The primary hypothesis to be tested is that BMT+EVT in stroke MeVO patients within the protocol-defined 12-hour onset/reference-time window, reduces disability at 90 days as determined by the mRS scale.

2.7. Eligibility

Inclusion

- Age 18–80; pre-stroke mRS 0–1.

- Baseline NIHSS ≥ 9 and ≤ 17 .
- Onset-to-randomization time < 12 hours; for wake-up strokes, < 12 hours from the sleep midpoint; for other unwitnessed strokes, < 12 hours from last known well.
- Isolated MeVO on CTA/MRA: non dominant M2–M3, A2–A3, P2–P3.
- ASPECTS ≥ 6 on NCCT. When AI-based NCCT core-volume assessment is available, AI-ICV must be < 10 mL. When CTP is available, the volume of hypoperfused tissue with Tmax > 6 seconds must be > 30 mL.
- Informed consent (patient or LAR).
- In patients eligible for intravenous thrombolysis, enrollment may proceed only if the NIHSS score remains between 9 and 17 (inclusive) 30 minutes after initiation of intravenous thrombolysis.

Exclusion

- Proximal LVO (ICA, M1) or tandem cervical ICA stenosis $> 70\%$.
- Intracranial hemorrhage at baseline.
- Life expectancy < 3 months.
- Severe allergy to iodinated contrast

2.8 Outcomes

Primary efficacy outcome

- Functional independence (mRS 0–2) at 90 days.

Secondary efficacy outcomes (no recanalization endpoints)

- Ordinal mRS shift at 90 days.
- mRS 0–1 at 90 days.
- Early NIHSS improvement at 24h (Δ NIHSS ≥ 8 or 24h NIHSS ≤ 2).
- 24–48h infarct volume (mL) by core lab.
- Discharge disposition (home vs facility); hospital length of stay.
- EQ-5D-5L at 90 days; return to work/activities at 90 days.

- 90 days PROMs assessment evaluating different specific domains. (PROMs Scales)

Safety outcomes (separate)

- Symptomatic intracranial hemorrhage (sICH), defined according to ECASS-III criteria, within 24–36 h. Hemorrhagic findings on follow-up imaging will be categorized according to the Heidelberg Bleeding Classification.
- Any ICH; radiological hemorrhage classification by the core lab according to the Heidelberg Bleeding Classification.
- Embolization to new territory (ENT).
- Subarachnoid hemorrhage related to procedure.
- Vessel perforation/dissection; vasospasm requiring treatment.
- Access-site complications needing intervention/transfusion.
- Device/procedure-related serious adverse events.
- All-cause mortality at 90 days.
- Serious adverse events (SAEs) through 90 days.

Exploratory angiographic/physiologic endpoints (non-efficacy)

- Angiographic reperfusion on final run (eTICI 2b/7/2c/3), adjudicated by core lab.
- Successful anatomical access to target segment (ability to deliver aspiration catheter/stent-retriever to clot).
- First-line EVT technique used.
- First-pass effect (FPE; eTICI 2c/3 after a single pass by technique used) and number of device passes or infused thrombolytic drug.
- Impact of vessel tortuosity parameters (automatically assessed with proprietary software: ARTERIAL) on safety (sICH, Subarachnoid hemorrhage) and efficacy (FPR, final recanalization, procedural length) parameters.
- Need for SAIL/other therapy and intra-arterial fibrinolytic/antiplatelet dose/exposure (total mg and duration).
- Target-vessel patency at 24–48 h on available follow-up CTA/MRA (AOL/TIMI-like recanalization categories), core-lab adjudicated; exploratory and assessed only among patients with available follow-up vascular imaging.

- Time metrics: puncture-to-final-angiogram and randomization-to-final-angiogram.
- Clot migration from CTA to DSA after IVT therapy (Treatment group).
- Spontaneous recanalization stratified by IVT (Control group)

2.9 Imaging & Assessments

- **Baseline:**

NCCT/MRI: NCCT ASPECTS; when AI-based NCCT core-volume assessment is available, AI-ICV <10 mL is required for eligibility.

CTA/MRA (arterial occlusion location)

CTP, when available: hypoperfused tissue volume with Tmax >6 s must be >30 mL for eligibility.

- **24–48h:**

NCCT or MRI for infarct volume and hemorrhage classification.

Follow-up vascular imaging (CTA/MRA) is not mandatory and may be performed according to local clinical practice; when available, it will be used for exploratory target-vessel patency assessment.

- Clinical: NIHSS baseline, 24h, day 7/discharge; mRS, EQ-5D-5L, and PROMs at 90 ± 14 days.

2.10 Statistical Analysis Plan

Primary Efficacy Analysis

Analysis Population

The primary efficacy analysis will be conducted in the **intention-to-treat (ITT)** population, defined as all randomized participants analyzed according to their randomized treatment assignment, irrespective of treatment received or protocol deviations.

Supportive populations: a per-protocol analysis will include participants analyzed according to randomized assignment after exclusion of prespecified major protocol deviations that materially affect eligibility or treatment exposure. A separate as-treated analysis will analyze participants according to the treatment actually received, irrespective of randomized assignment.

Primary Endpoint

The primary endpoint is functional independence at 90 days, defined as a modified Rankin Scale (mRS) score of 0–2, assessed at 90 ± 14 days after randomization and analyzed as a binary outcome (yes/no).

Primary Estimand

The primary estimand is the treatment effect of endovascular treatment (EVT) versus control on the probability of achieving mRS 0–2 at 90 days in the ITT population.

Primary Analysis Model

The primary analysis will use a logistic regression model with treatment group as the main explanatory variable. The model will adjust for center and the prespecified randomization stratification factors: age group (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and intravenous thrombolysis use (yes/no). The treatment effect will be expressed as an adjusted odds ratio (OR) with a two-sided 95% confidence interval. The overall two-sided type I error will be controlled at 0.05 according to the prespecified interim-analysis alpha-spending procedure.

Prespecified Covariates for Supportive Adjusted Analysis

The following baseline covariates, all measured prior to randomization, will be included in a prespecified supportive adjusted analysis:

- Age (years, continuous)
- Baseline NIHSS score (continuous)
- Baseline mRS (0 vs 1–2)
- AI-predicted infarct core volume on non-contrast CT (AI-ICV, continuous, mL)
- Time from symptom onset or last-known-well to randomization (minutes, continuous)
- Occlusion location (M2 vs non-M2)
- Use of IVT

Continuous covariates will be entered using linear terms without data-driven transformation or selection.

Adjustment for Center and Randomization Stratification Factors

Randomization is performed using permuted blocks within center and is stratified by:

1. Age group (≤ 70 vs > 70 years),
2. Occlusion territory (MCA vs ACA/PCA),
3. Use of intravenous thrombolysis (IVT); yes/no.

In the primary analysis, center and the original randomization stratification factors will be included as covariates in the regression model: age group (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and IVT use (yes/no).

Handling of Missing Data

If the primary endpoint (90-day mRS) is missing, multiple imputation under a missing-at-random (MAR) assumption will be used. The imputation model will include treatment group, center, randomization stratification factors, prespecified baseline prognostic covariates, and available post-randomization variables predictive of outcome or missingness. The primary analysis will be performed across imputed datasets and combined using Rubin's rules.

Supportive, Sensitivity, Subgroup, and Exploratory Analyses

Prespecified supportive and sensitivity analyses will include:

1. An unadjusted comparison of treatment groups using logistic regression with treatment group only.
2. An adjusted analysis including the original age stratification factor (≤ 70 vs > 70) instead of continuous age.
3. A complete-case analysis of the primary endpoint (all cases with a missing primary outcome are excluded).
4. As-treated analysis, with participants analyzed according to treatment actually received, irrespective of randomized assignment.
5. Prespecified subgroup analysis by IVT use (yes/no), assessed using a treatment-by-subgroup interaction term.
6. Prespecified subgroup analysis by stroke etiology (ICAD vs other), assessed using a treatment-by-subgroup interaction term.
7. Prespecified subgroup analysis by baseline NIHSS, assessed using a treatment-by-subgroup interaction term.

8. Exploratory procedural analysis comparing SAIL versus ADAPT among EVT-treated patients; this is a non-randomized comparison and will be interpreted as exploratory.
- Secondary efficacy: The secondary endpoint (ordinal mRS at 90 days) will be analyzed using a proportional odds model including treatment group and the above prespecified baseline covariates. The treatment effect will be reported as the adjusted common odds ratio with a two-sided 95% CI; interpretation will respect the prespecified hierarchical testing procedure and overall type I error control.
 - **Safety:** incidence and risk differences in sICH and mortality; DSMB-defined boundaries for harm and stopping rules.
 - **Multiplicity:** hierarchical testing (primary → mRS shift → mRS 0–1). Others exploratory.
 - Interim analyses: safety-only reviews of sICH and mortality after every 100 patients recruited; one interim efficacy/futility analysis at approximately 50% recruitment. The overall two-sided type I error rate will be controlled at 0.05 using an O’Brien–Fleming alpha-spending approach; nominal significance levels at interim and final analyses will follow the prespecified alpha-spending function.
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2.11 Monitoring & Governance

- Independent DSMB; blinded Clinical Events Committee; central imaging core. The DSMB will periodically review safety events, including intracranial hemorrhage and procedure-related complications, and may evaluate whether vascular tortuosity or other anatomical characteristics are associated with increased procedural risk. Based on these reviews, the DSMB may recommend continuation without modification, protocol modification, temporary suspension, or termination for safety reasons. Any modification to eligibility criteria will require a formal protocol amendment and appropriate ethics/regulatory approval before implementation.
- Site credentialing for MeVO EVT and SAIL.
- Adherence tracking (screening log, crossovers, protocol deviations).

2.12 Ethics & Dissemination

- Conduct under the Declaration of Helsinki and ICH-GCP.
 - Prior IRB/ethics approvals at all sites; informed consent process (patient/LAR).
 - Trial registration prior to first patient.
 - Results disseminated via peer-reviewed publications and conference presentations.
-

2.13 Timeline (indicative)

Preparation (3 mo) → Enrollment (24 mo) → 90-day follow-up (3 mo) → Analysis & manuscript (6 mo).

2.14 Study assessments

The study assessments include:

1. Screening/consenting/baseline history and exam.
2. Randomization
3. Procedure/treatment data.
4. 24-hour (12-48 hours) post-randomization data.
5. Day 5 $\pm$ 1 post-randomization or hospital discharge data.
6. 30-day follow-up visit $\pm$ 7 days.
7. 90-day follow-up visit $\pm$ 30 days.

Imaging analysis: CT/MR/DSA per central core lab blinded to clinical outcomes.

2.15 Participating sites

Up to 10 large volume Comprehensive Stroke Centers.

3. Introduction.

3.1 Study rational and background.

Endovascular treatment (EVT) is firmly established as standard care for acute ischemic stroke due to proximal large-vessel occlusion (LVO)(1). In contrast, the benefit of EVT for medium/distal vessel occlusions (MeVO) remains uncertain. Several recent randomized trials in MeVO populations (2-4) have failed to demonstrate a clear overall clinical advantage of EVT over best medical management. These neutral findings have prompted scrutiny of trial design and execution, and particularly the characteristics of the patients enrolled.

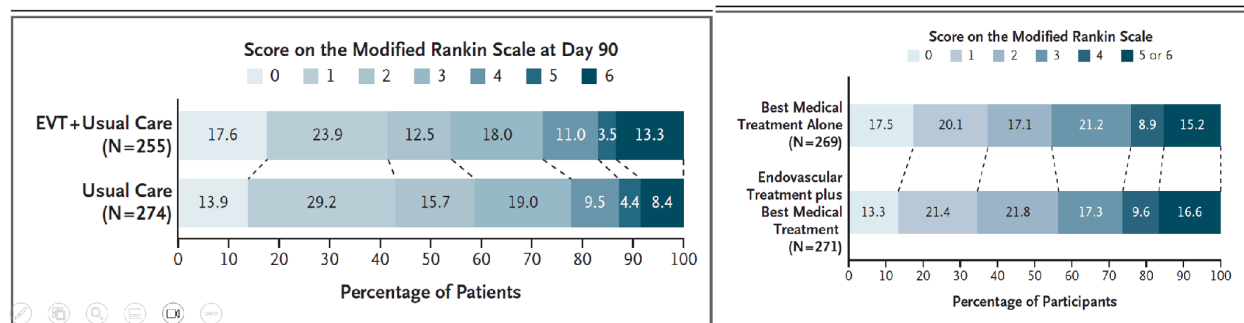


Figure: Results of the Escape Mevo and Distal trials

Several, non-exclusive explanations have been proposed for these results. First, inclusion and exclusion criteria may have been insufficiently selective, allowing enrollment of patients in whom the absolute benefit of recanalization is small. Second, MeVOs encompass heterogeneous vascular territories and vessel calibers, where current thrombectomy devices may have variable efficacy and risk profiles across these anatomies (4). Third, variability in imaging selection (non-contrast CT, CT perfusion, and differing thresholds or vendors for core and hypoperfusion calculation) and clinical heterogeneity (age, baseline NIHSS, time from onset to imaging) can dilute a treatment signal when analyzed in aggregate. Additional contributors likely include operator and center variability, and the statistical penalties of modest sample sizes in subgroup-rich trials.

Despite these complexities, there is little doubt that successful recanalization (eTICI 2b–3) is, in general, associated with better outcomes (4). In virtually all centers performing EVT, technical success is achieved in a high proportion of patients, consistent with contemporary practice. The rate of successful recanalization is however

lower among Mevo patients as compared to stroke patients with a large vessel occlusion, pointing to the fact that specific devices and techniques should be further developed to improve the efficacy of EVT in Mevo patients. Moreover, the clinical benefit of recanalization is unlikely to be uniform across all MeVO patients. If a sizable subset has little or no incremental gain from reperfusion, their inclusion in trials can dilute the average treatment effect and render studies statistically neutral despite meaningful benefit in the right patients (5).

These considerations argue for enrichment strategies—pre-specified clinical and imaging criteria— designed to identify the MeVO patients that most likely will benefit from EVT and reject those who will not. Candidate effect modifiers include baseline neurological severity (NIHSS), age, onset-to-imaging time, and imaging markers such as early ischemic signs, predicted infarct core or hypoperfused volume. By refining eligibility using these readily available variables, future trials may enhance statistical power to detect clinically relevant differences while preserving generalizability.

3.2 Population Optimization

A recent study from our group suggests that the treatment effect of recanalization in patients with acute ischemic stroke due to MeVO is strongly influenced by both clinical and radiological factors (6). In particular, variables such as age, baseline NIHSS, and imaging parameters reflecting ischemic core and hypoperfused tissue volumes markedly modified the observed benefit of successful reperfusion. These findings underscore the heterogeneity of treatment response within this patient population and support the concept that individualized selection based on baseline characteristics and imaging profiles may optimize the clinical impact of endovascular therapy in distal occlusions.

Applying each of the individual enrichment criteria would result in a notable enhancement of the treatment effect, though at the expense of a moderate reduction in the proportion of patients retained. This reflects the balance between maximizing therapeutic benefit and maintaining generalizability. The effect may be substantially magnified when multiple enrichment rules are applied in combination, yet this comes at the cost of a markedly lower patient retention rate, highlighting the trade-off between selectivity and applicability in optimizing candidate selection for distal EVT. (figure 1)

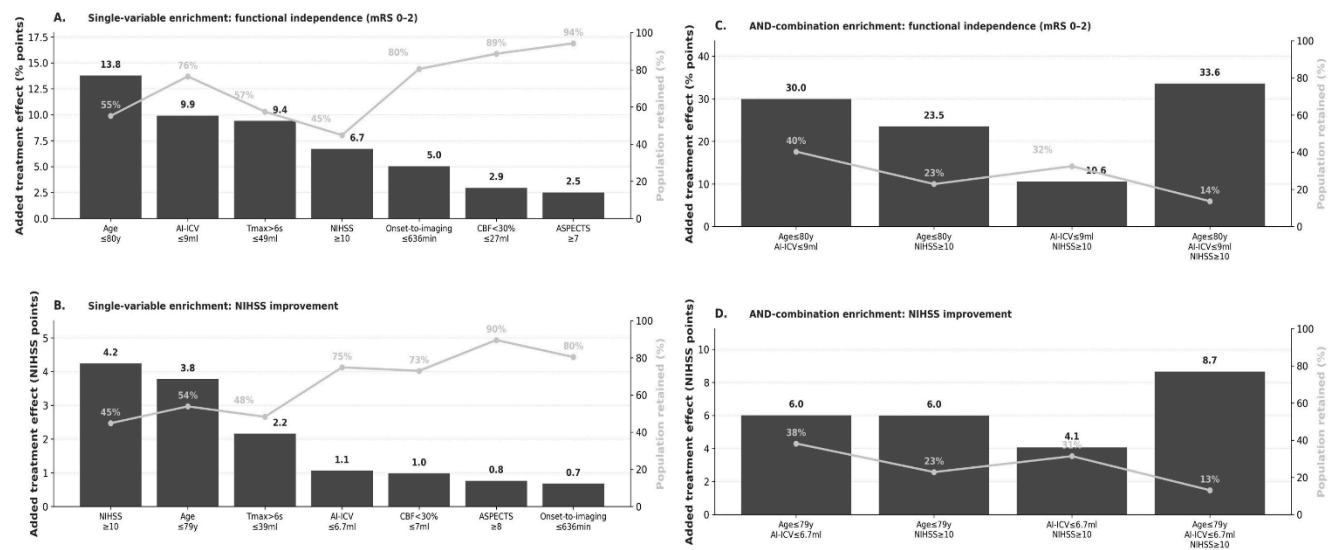


Figure 1

Enrichment and safety analyses summarizing how clinical and imaging variables modify efficacy. A: Added treatment effect (ΔTE) for achieving mRS 0–2 at 90 days, by enrichment variable and their AND combinations (C), with corresponding retained population (%). Panel B: Added treatment effect on NIHSS improvement (Admission – Discharge) compared with the whole population by enrichment variable and their AND combinations (D).

Previous studies have demonstrated that infarct size exerts a stronger influence on functional recovery in older patients (9). While in large vessel occlusions, older individuals may still experience meaningful clinical improvement when recanalization is achieved (10), the scenario differs in distal vessel occlusions, where the potential infarct volume is inherently smaller. In this context, the relative functional impact of even limited ischemic injury may be greater in elderly patients, which may attenuate the observable benefit of recanalization on clinical outcomes. For these reasons the design of future trials, such as the present one, aiming to assess the efficacy of EVT in MeVO stroke patients should avoid the inclusion of older patients with an already established infarct core on admission (figure 2).

Regarding baseline NIHSS, not only is it more challenging to demonstrate a significant impact on clinical recovery when symptoms are mild, but doing so also requires larger patient cohorts to achieve sufficient statistical power. Moreover, distal vessel occlusions often involve isolated, different, functionally distinct vascular territories (4), leading to heterogeneous clinical presentations that may not be fully captured by global disability scales such as the NIHSS or mRS. Impairments in domains such as fatigue,

depression, cognitive decline, or anxiety can only be adequately assessed through specific patient-reported outcome measures (11), which are rarely included in acute stroke trials. In contrast, large vessel occlusions typically involve extensive brain regions and produce severe, homogeneous neurological deficits that are more faithfully reflected by conventional scales like the NIHSS and mRS, making these tools particularly suitable for assessing recovery in strokes due to proximal occlusions. On the other hand, our results show a decline in the treatment effect of recanalization among patients admitted with very high NIHSS score on admission (figure 2). In these cases, the observed severe neurological symptoms may be related to a prior proximal occlusion location that has migrated distally by the time of imaging acquisition, with no parallel symptom improvement. Therefore, the arterial status of the distal occlusion observed on admission may not fully reflect clinical evolution. For this reason, excluding the patients admitted with MeVO and very high NIHSS on admission from clinical trials may also help optimize the population in which the treatment effect of EVT is greater.

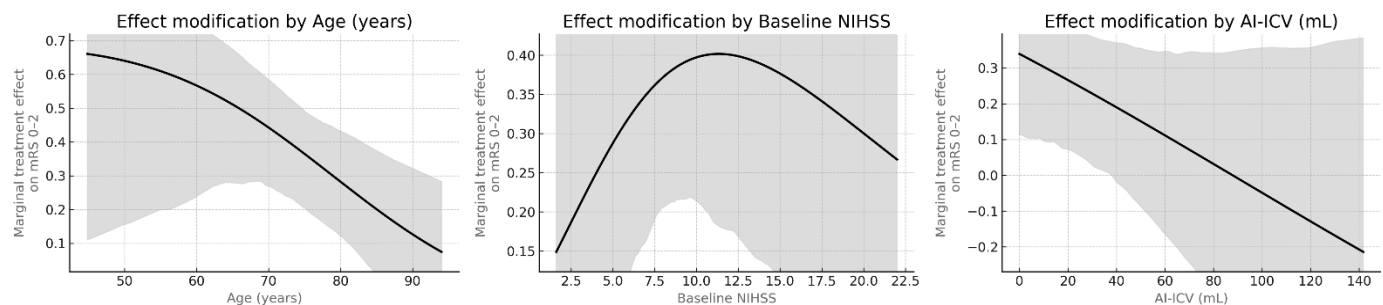


Figure 2.

*Model-based effect modification plots showing the marginal treatment effect of recanalization on functional independence (mRS 0–2) across continuous ranges of **Age (A)**, **Baseline NIHSS (B)**, and **AI-derived ischemic core volume (AI-ICV) (C)**. Solid black lines represent estimated marginal effects, and shaded gray areas indicate 95 % confidence intervals derived from the model’s covariance matrix.*

In our previous studies, the hypoperfused volume (Tmax > 6 s on admission CTP)—which classically correlates with the concomitant NIHSS score as it reflects the extent of dysfunctional but potentially salvageable brain tissue—did not emerge as a factor capable of modifying the treatment effect of recanalization. Larger hypoperfused volumes were not necessarily associated with a greater clinical impact of reperfusion. Consequently, mismatch-based thresholds that rely on the Tmax > 6 s concept did not yield the greatest increases in treatment effect in our enrichment analyses. This finding suggests that the usual perfusion thresholds established for large vessel occlusions

(LVOs) to define hypoperfused tissue at risk may not be directly applicable to distal occlusions (12). Future studies should determine whether alternative, MeVO-specific thresholds for perfusion delay can better delineate tissue at risk and identify the subgroup of patients most likely to benefit from endovascular treatment. Concerning the predicted infarct core, excluding patients with larger, already irreversibly established lesions naturally enhances the observed treatment effect of recanalization. This is particularly relevant in cases of secondary distal occlusions, which often represent partially recanalized proximal occlusions (either spontaneously or after iv thrombolysis), where a deep infarct within the M1–MCA perforator territory may already be established before partial recanalization leads to distal branch occlusion. The apparent superiority of AI-derived ischemic core volume on non-contrast CT (AI-ICV, automatically assessed with infarct core module developed by Methinks, Spain) in magnifying the treatment effect—compared with CT perfusion (CTP)-based estimates—may be explained by the limitations of perfusion imaging in this partial reperfusion setting. Specifically, CTP may yield false-negative predictions in previously reperfused regions corresponding to earlier proximal occlusions or may exhibit reduced accuracy of the Cerebral Blood Flow thresholds, originally validated for large vessel occlusions, which may not accurately reflect tissue fate in distal occlusions (12,13).

Beyond improving efficacy, the optimization of patient selection for EVT based on the identified clinical and imaging characteristics may also enhance safety outcomes by reducing the risk of symptomatic intracranial hemorrhage (sICH). Patients with favorable profiles—such as younger age, smaller ischemic cores, and limited hypoperfusion volumes—are less likely to experience reperfusion-related complications once recanalization is achieved. An exception was observed for baseline NIHSS, where more severe strokes were associated with greater treatment effects but without a corresponding reduction in the risk of sICH. This may be explained by the disproportionate impact of lesion location on clinical severity in distal occlusions, where NIHSS reflects not only infarct extent but also the functional significance, eloquence and strategic location of the ischemic territory. Beyond infarct characteristics, in strokes secondary to MeVO, the risk of symptomatic intracranial hemorrhage is strongly modulated by interindividual differences in the cerebral angioarchitecture and vessel tortuosity, factors that can heighten procedural difficulty and predispose to technical complications during EVT. A recent study showed that vascular tortuosity features automatically assessed with an AI-based software may help identify the patients in which reaching the occlusion requires catheterization of severely tortuous vessels (14). Such tool could be implemented in the screening algorithm in order to identify the population in which EVT for MeVOS stroke is safer.

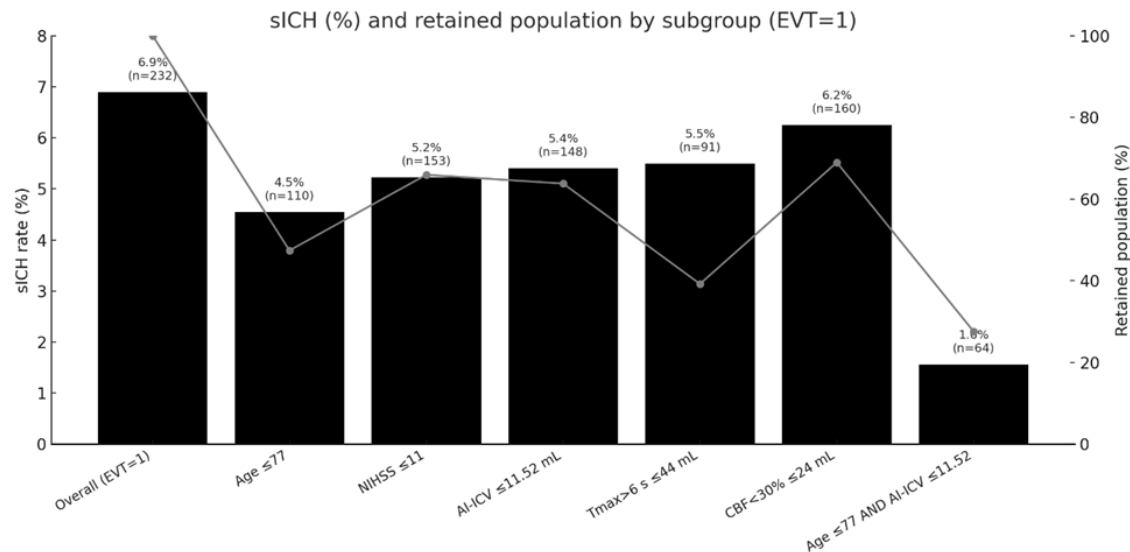


Figure 3

Rates of symptomatic intracranial hemorrhage (sICH) according to enrichment rules and retained patient proportions.

Our findings provide valuable insights for the design of future clinical trials aimed at establishing the benefit of endovascular therapy (EVT) for distal vessel occlusions.

The study provides new evidence that the clinical benefit of recanalization in distal vessel occlusions is highly dependent on patient-specific clinical and radiological features. Refining selection criteria through these enrichment variables may allow more precise identification of patients most likely to benefit from endovascular therapy, while improving overall safety and interpretability of treatment outcomes. These insights served as a foundation for the design of the present trial.

3.3 Justification for use of Automatic volume detection on Plain NCCT

Recently, there has been an increased spread of automated software evaluating NCCT to detect stroke and support decision making. Studies have shown that the imaging changes in Non-Contrast CT (NCCT) after AIS become more apparent with time but can be detected and quantified very early with deep learning based algorithms. This could be a suitable option given the general availability across the globe, low cost, less treatment delays, technical simplicity, and ease of interpretation. Furthermore,

advanced imaging such as CTP can incorrectly over/infraestimate the infarct core volume, which can lead to an inappropriate exclusion of some patients from treatment.

The Methinks Suite (Methinks Software S.L. Barcelona, Spain) utilizes a deep learning algorithm to recognize LVO patterns and predicted infarct core volume using NCCT. The tool has shown promising results in automatically predicting LVO when compared to CTA evaluated by neuroradiologist (**figure 4**). Recent published data showed that the algorithm could be further trained to also estimate the amount of infarct core volume using an artificial intelligence protocol (7). The ischemia assessment on NCCT (aICV) on admission was validated on 320 patients with follow-up MRI scans (24/48 hours after stroke onset). The aICV measurement on admission NCCT showed similar correlations to final infarct on MRI DWI images as the widely used CT perfusion imaging core (CBF <30%) estimations and higher than ASPECTS readings by experts on NCCT (**table 1 and figure 5**). A subsequent study showed a clear relation between aICV and long-term functional outcome in patients receiving reperfusion treatments (**figure 6**). The algorithm's robust performance holds significant potential in settings with limited access to advanced imaging technologies across diverse healthcare environments.

	Adjusted Pearson correlations
Ground truth interobserver FIV on DWI	0.81
Perfusion CBF<30% - FIV on DWI	0.51
Manual NCCT ASPECTS- FIV on DWI	(-) 0.25
Methinks NCCT-Ischemia- FIV on DWI	0.50

Table 1: Results from the NCCT-ischemia non-viable tissue estimation.

Ortega-Gutierrez S, Stroke Vasc Intervent Neurol 2024

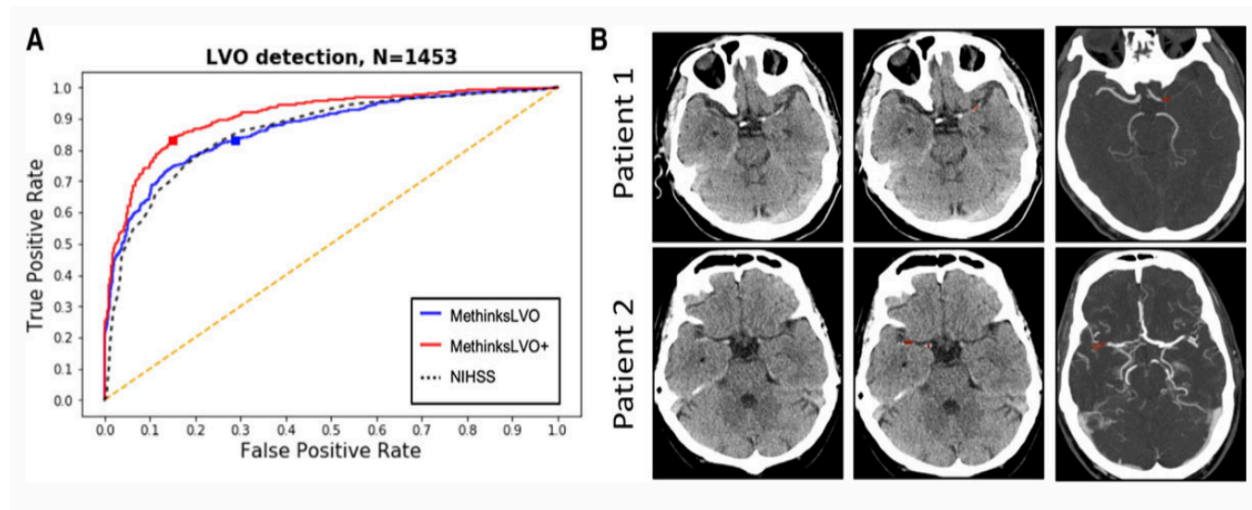


Figure 4: A, Area under the curve for large vessel occlusion (LVO) detection of MethinksLVO and MethinksLVO+ compared with National Institutes of Health Stroke Scale scores. B, Examples of LVO detection on non-contrast computed tomography showing: original scan, automated detection with clot marked in red and manually tagged computed tomography angiography, respectively. (*Reproduced from Olive-Gadea, 2020*)

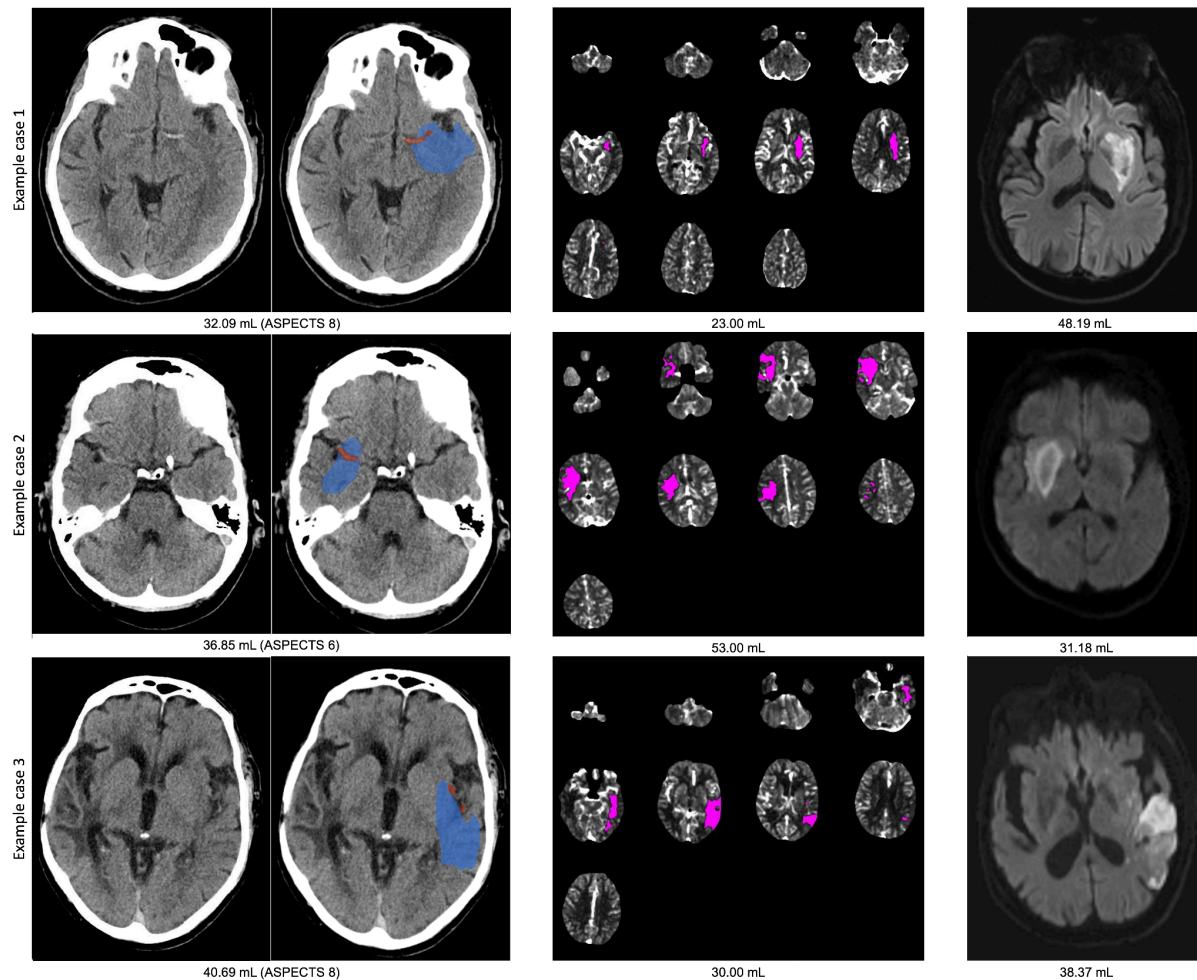


Figure 5. Illustration of 3 cases showing the performance of the Methinks automatic algorithm versus ICV-CTP and FIV-DWI. Each corresponds to a different patient, illustrating the same anatomical region of the brain but not necessarily the exact same slice. First Column - Baseline CT and Predicted Map from Methinks algorithm: This column shows a plain slide of the patient CT and the infarct core volume predictions made by our algorithm using non-contrast computed tomography. Second Column - Predicted Map from RAPID estimated core volume on CTP: Here, the images are generated from CT perfusion scans processed by the RAPID software, which predicts infarct core volumes measuring an absolute CBF < 30%. Third Column - Ground Truth on MRI DWI sequence: These images are from Diffusion-Weighted Imaging, considered the gold standard for identifying acute ischemic changes in the brain. On the bottom of each image the estimation of ischemic core volume in mL and ASPECT is shown. The represented slices are not exactly the same, as the different types of acquisitions have different numbers of slices and are chosen to best depict the algorithm's prediction capabilities.

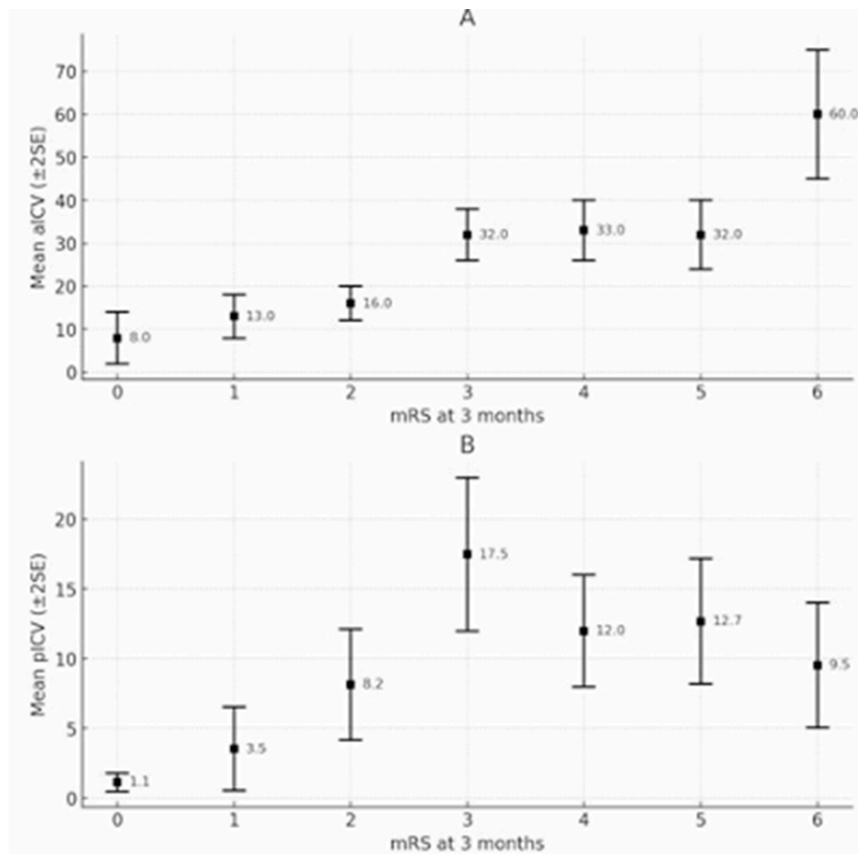


Figure 6. Relationship of ICV with functional outcome. Mean (SE) in mL for (A) aICV, (B) pICV according to the modified Rankin Score (mRS) at 3 months. aICV, automated initial core volume in NCCT-Methinks; pICV, initial core volume by CTP. Flores A, et al. *J NeuroIntervent Surg* 2025

4. Objectives and Hypotheses

SAIL-MeVO is a phase III prospective, randomized-controlled trial in which stroke MeVO patients will be allocated to receive BMT Vs BMT+EVT. This will provide further evidence on whether EVT is safe and reduces disability at 90 days as compared with BMT alone. A series of clinical and radiologic inclusion/exclusion criteria will be applied to optimize the study population to include only patients in which the estimated treatment effect of EVT is presumed maximal. The EVT arm protocol will include also an optimization of the techniques in order to minimize the mechanical impact on the vascular angioarchitecture including optimized intra-arterial arterial lysis drug delivery method (SAIL) when direct access with an aspiration catheter is not easily achievable.

Primary Aim: Determine whether EVT improves functional independence at 90 days (mRS 0–2) versus BMT in MeVO stroke patients.

Secondary objectives (efficacy only; no recanalization endpoints): (i) ordinal mRS shift at 90d; (ii) excellent outcome mRS 0–1 at 90d; (iii) Dramatic neurological improvement at 24h (Δ NIHSS ≥ 8 or 24h NIHSS ≤ 2); (iv) infarct volume at 24–48h; (v) discharge disposition & length of stay; (vi) EQ-5D-5L at 90d + Domain specific PROMS; (vii) return to work/activities at 90d.

Study Design

Overall design: Prospective, randomized, open-label with blinded endpoint assessment (PROBE). Patients presenting with symptoms of AIS and confirmed MeVO on admission CTA, NIHSS ≥ 9 and ≤ 17 , and within the protocol-defined <12-hour onset/reference-time window will be assigned to receive BMT Vs BMT+EVT

Participating sites: Up to 10 comprehensive stroke centers will be selected to participate in the trial.

Study duration: Active enrollment is expected to last approximately 24 months. The total study duration is expected to be approximately 30 months, allowing for site initiation, 90-day follow-up, and close-out.

Study population: eligibility

Inclusion criteria

- Age 18–80; pre-stroke mRS 0–1.
- Baseline NIHSS ≥ 9 and ≤ 17 .

For patients receiving intravenous thrombolysis before randomization, the NIHSS score used to determine eligibility will be obtained 30 minutes after initiation of intravenous thrombolysis and must remain between 9 and 17, inclusive.

- Onset-to-randomization <12 hours; for wake-up strokes, <12 hours from the sleep midpoint; for other unwitnessed strokes, <12 hours from last known well
- Isolated MeVO on CTA/MRA: **non dominant M2–M3, A2–A3, P2–P3.**
- ASPECTS ≥ 6 on NCCT. When AI-based NCCT core-volume assessment is available, AI-ICV must be <10 mL. When CTP is available, the volume of hypoperfused tissue with Tmax >6 seconds must be >30 mL.
- Informed consent (patient or LAR).

Exclusion criteria

- Proximal LVO (ICA, M1) or tandem cervical ICA stenosis >70%.
- Intracranial hemorrhage at baseline.
- Pregnant women
- Life expectancy <3 months.
- Severe allergy to iodinated contrast

For patients who undergo multiple imaging studies, the most recent imaging study will be used for trial eligibility. Similarly, for patients with multiple NIHSS scores, the last one prior to randomization will be used for trial eligibility. For patients who are sedated or intubated, the last NIHSS score obtained prior to sedation or intubation should be used.

Screening log

- A Screening and Enrollment Log will be maintained by the site to document basic information such as date screened and reason for screen failures for subjects who fail to meet the study eligibility criteria. Screen failed subjects and their reason(s) for screen failure will be documented and may be entered into an electronic database, but they will not be followed beyond the screening visit, and no further data will be collected/recorded.

Informed Consent

- Written informed consent will be obtained from all participants prior to enrollment in the SAIL-MeVO trial. Whenever possible, informed consent will be obtained directly from the patient before any study-specific procedures are initiated. If the patient lacks decision-making capacity due to the acute nature of ischemic stroke, informed consent will be obtained from a legally authorized representative or a designated person of trust, in accordance with local laws and regulations.
- In situations where neither the patient nor a legally authorized representative or person of trust is available, and if approved by the local ethics committee and permitted by national regulations, the investigator may enroll the patient using emergency informed consent procedures. In such cases, enrollment will be based on the investigator's judgment that the patient meets all eligibility criteria and that participation is in the patient's best interest. As soon as feasible after enrollment, the patient and/or their legally authorized representative will be informed about the trial, and written informed consent will be sought for the continuation of participation in the study. If consent is subsequently refused, the participant will be withdrawn from the study in accordance with the protocol and applicable regulations.

5. Randomization and allocation

Eligible participants will be randomized in a 1:1 allocation ratio to receive either best medical treatment alone (BMT) or endovascular treatment plus best medical treatment (EVT+BMT). Randomization will be implemented through a centralized,

secure, web-based randomization system, ensuring allocation concealment and full traceability in accordance with the European Union Clinical Trial Regulation (EU) No 536/2014 and ICH-GCP requirements.

Randomization will use permuted blocks within each participating center, with block sizes concealed from investigators. Allocation will be stratified by prespecified baseline factors: age (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and use of intravenous thrombolysis (yes/no). Center and all randomization stratification factors will be prespecified and included as covariates in the primary efficacy analysis model.

After obtaining informed consent, patients will be randomized. All subjects with a signed informed consent form (ICF) are considered enrolled in the study. The intention to Treat Population (ITT) will be considered as those that were randomized. Subjects with a signed ICF but who are not randomized will undergo routine imaging evaluation and receive standard therapy according to local guidelines. Baseline data and information about early stroke therapies will be captured for this group of patients. The reason for no randomization will also be recorded.

Subjects with a signed ICF who are randomized (Intention to Treat population, ITT) will be followed for the entire study duration (3-months post enrollment). Only and all subjects who are randomized will be included in the primary efficacy analysis.

Blinding

Due to the nature of the interventions, the SAIL-MeVO trial will be conducted as an open-label study with respect to treatment allocation. Treating physicians, interventionalists, and site study personnel involved in the delivery of best medical treatment and endovascular procedures will not be blinded to treatment assignment.

To minimize assessment bias, blinded outcome assessment will be implemented. Functional outcome at 90 days, including the modified Rankin Scale (mRS), will be

assessed by trained personnel who are independent of the treating team and blinded to treatment allocation. Imaging endpoints will be evaluated by an imaging central core laboratory with readers blinded to treatment assignments and clinical outcomes. Statistical analyses will be conducted according to a prespecified Statistical Analysis Plan; whenever feasible, the primary analysis will be performed with treatment groups coded to maintain blinding of the statistician until the analysis database is locked.

Emergency unblinding procedures are not applicable, as treatment allocation is known to the treating teams. Any deviations from blinded outcome assessment will be documented and reported.

Study Interventions

Control (BMT): Guideline-based medical therapy, including IV thrombolysis when indicated.

Experimental arm (EVT+BMT): Patients allocated to the experimental arm will follow the stepwise EVT protocol:

1-ADAPT – preferred first-line aspiration when the catheter can be safely and readily advanced to the target occlusion; maximum two aspiration attempts before transition to SAIL

2-SAIL – may be used first-line when anatomy is unfavorable for safe distal aspiration-catheter navigation, or as rescue after failure of ADAPT (maximum two aspiration attempts). Permitted agents are alteplase, tenecteplase, tirofiban, or eptifibatide (Integrilin), according to protocol dosing.

Procedural details (catheter models, wire/guide selection, lysis dosing windows, and stop rules) will be specified in the Operations Manual/Appendix.

Each treated patient will be followed and assessed 3 months after randomization by an independent investigator blinded to allocated arm.

Concomitant treatments: The use of intra-arterial vasodilators (such as nimodipine) is allowed and will be recorded.

Prohibited treatments: the use of experimental endovascular devices or drugs is not allowed.

Crossover and rescue therapy rules. For the primary analysis cross overs will be

considered as initially allocated (ITT) and as treated in the secondary per protocol analyses.

Protocol deviations related to treatment: all protocol deviations related to treatment, particularly the use of mechanical thrombectomy devices differently than specified in the Operations Manual will be recorded.

STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

Patient Screening and Enrollment

The study team will be contacted by the clinician providing care for all acute ischemic stroke patients so that they will be screened for SAIL-MeVO trial eligibility. Patients meeting all the inclusion criteria and none of the exclusion criteria are eligible for enrollment into SAIL-MeVO. A detailed screening log of patients evaluated but not enrolled will be kept.

The study assessments are shown in table 2 and include:

Clinical

Baseline assessments: screening/consenting/baseline history (demographics and relevant past medical history) and neurological exam (NIHSS score on admission).

Randomization: allocated treatment arm, received treatment.

Treatment phase assessments: treatment data: use of IVT and MT procedural details including initial TICl score, final TICl score, number of passes, devices and technique used, use and dose of intra-arterial lytics.

Post-treatment and follow-up assessments: 24-hour (12-48 hours) post-randomization data, day 5 $\pm$ 1 post-randomization or hospital discharge data, 30-day follow-up visit $\pm$ 7 days, 90-day follow-up visit $\pm$ 15 days.

IMAGING

Imaging analysis: CT/CTA/CTP/MRI-MRA/DSA per central core lab blinded to clinical outcomes.

Baseline NCCT

Presence of intracranial hemorrhage (ICH), established infarct (hypodensity), ASPECTS score and automated infarct core volume prediction (Methinks Suite).

Baseline CTA: MeVO identification

Identification and location on admission CTA of LVO / MeVO: non dominant M2–M3 segments of the MCA, A2–A3 segments of the ACA or P2–P3 segments of the PCA are eligible for the study.

Baseline CTP (optional)

Predicted infarct core volume and hypoperfusion volume (Tmax >6 s) will be recorded when available.

Follow-up NCCT/MR (24±12 hours)

Identification of intracranial hemorrhage (classified per Heidelberg criteria as HI-1, HI-2, PH-1, PH-2), Subarachnoid hemorrhage, FIV.

Additional Imaging

Additional neuroimaging studies performed as standard of care, will be anonymized and sent to the imaging core lab for secondary analysis. However, they should not delay patient consent and randomization.

Assessment/ Action	Baseline	EVT Immediate Post-treatment	24 hours (16-36 hours)	Day 5 (± 1 day) or Discharge	30 days (± 7 days)	90 days (± 30 days)
Demographics/Medical History	X					
Blood labs*	X*					
Inclusion/Exclusion Criteria	X					
Informed Consent	X					
NCCT/CTA (MRI/MRA)/CTP (optional)	X°		X°			
Randomization	X					
Vital Signs	X	X	X	X		
NIH Stroke Scale	X		X	X		
Modified Rankin Scale	X			X	X	X

Discharge Disposition				X		
Procedure Details		X				
TICI score (baseline, first pass, final)		X				
ICH Classification~			X	X		
Adverse Events & SAE		X	X	X	X	X
EQ-5D-5L^ PROMS						X^

Table 2: study assessments. *Platelets, INR (for patients on warfarin) and activated PTT (for patient on heparin or novel anticoagulants), and pregnancy test (if applicable).

° NCCT must be performed at baseline according to a site's standard of care. NCCT or MRI is mandatory at 24 hours and with any neurological deterioration of 4 points or more on NIHSS. CTP and CTA are not required at 24 hours, but will be collected if obtained. ~Using Heidelberg classification (Appendix B).

^EQ-5D-5L should be performed by the patient or care giver.

Outcomes and endpoint Definitions

Primary Hypothesis

The primary hypothesis to be tested is that BMT+EVT in stroke MeVO patients within 12 hours after symptom onset, reduces disability as compared with BMT alone at 90 days as determined by the mRS scale.

Outcomes

Primary efficacy outcome

- Functional independence (mRS 0–2) at 90 days.

Secondary efficacy outcomes

- Ordinal mRS shift at 90 days.
- mRS 0–1 at 90 days.
- Early NIHSS improvement at 24h (Δ NIHSS ≥ 8 or NIHSS ≤ 2).
- 24–48h infarct volume (mL) by core lab.
- Discharge disposition (home vs facility); hospital length of stay.
- EQ-5D-5L at 90 days; return to work/activities at 90 days.

- 90 days PROMs assessment evaluating different specific domains.(PROMs Scales)

Safety outcomes (separate)

6. Symptomatic intracranial hemorrhage (sICH), defined according to ECASS-III criteria, within 24–36 h. Hemorrhagic findings on follow-up imaging will be categorized according to the Heidelberg Bleeding Classification.
7. Any ICH; radiological hemorrhage classification by the core lab according to the Heidelberg Bleeding Classification.
8. Embolization to new territory (ENT).
9. Subarachnoid hemorrhage related to procedure.
10. Vessel perforation/dissection; vasospasm requiring treatment.
11. Access-site complications needing intervention/transfusion.
12. Device/procedure-related serious adverse events.
13. All-cause mortality at 90 days.
14. Serious adverse events (SAEs) through 90 days.

Exploratory angiographic/physiologic endpoints (non-efficacy)

- Angiographic reperfusion on final run (eTICI 2b/7/2c/3), adjudicated by core lab.
- Successful anatomical access to target segment (ability to deliver aspiration catheter/stent-retriever to clot).
- First-line ECT technique used.
- First-pass effect (FPE; eTICI 2c/3 after a single pass by technique used) and number of device passes or infused thrombolytic drug.
- Impact of vessel tortuosity parameters (automatically assessed with proprietary software: ARTERIAL) on safety (sICH, Subarachnoid hemorrhage) and efficacy (FPR, final recanalization, procedural) parameters.
- Need for SAIL intra-arterial fibrinolytic dose/exposure (total mg and duration).
- Target-vessel patency at 24–48 h on available follow-up CTA/MRA (AOL/TIMI-like recanalization categories), core-lab adjudicated; exploratory and assessed only among patients with available follow-up vascular imaging.

- Time metrics: puncture-to-final-angiogram and randomization-to-final-angiogram.
-

- 24–48 h: NCCT or MRI for infarct volume and hemorrhage classification. Follow-up CTA/MRA is not mandatory; when available, it will be used for exploratory target-vessel patency assessment.
- Clinical: NIHSS baseline, 24h, day 7/discharge; mRS and EQ-5D-5L at 90 ± 14 days.

Sample size determination.

Sample size: Assuming control arm mRS 0–2 rate at 90 days of 43% and 57% in the EVT arm ($\Delta=14\%$), $\alpha=0.05$, power=80% → $n=200/\text{arm}$ (1:1 Allocation ratio: 400 total); with 5% attrition → ~420 total.

13. Statistical Plan (high level)

Statistical Analysis Plan – Primary Efficacy Analysis

Analysis Population

The primary efficacy analysis will be conducted in the **intention-to-treat (ITT)** population, defined as all randomized participants analyzed according to their randomized treatment assignment, irrespective of treatment received or protocol deviations.

Supportive populations: a per-protocol analysis will include participants analyzed according to randomized assignment after exclusion of prespecified major protocol deviations that materially affect eligibility or treatment exposure. A separate as-treated analysis will analyze participants according to the treatment actually received, irrespective of randomized assignment.

Primary Endpoint

The primary endpoint is functional independence at 90 days, defined as a modified Rankin Scale (mRS) score of 0–2, assessed at 90 ± 14 days after randomization and analyzed as a binary outcome (yes/no).

Primary Estimand

The primary estimand is the treatment effect of endovascular treatment (EVT) versus control on the probability of achieving mRS 0–2 at 90 days in the ITT population.

Primary Analysis Model

The primary analysis will use a logistic regression model with treatment group as the main explanatory variable. The model will adjust for center and the prespecified randomization stratification factors: age group (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and intravenous thrombolysis use (yes/no). The treatment effect will be expressed as an adjusted odds ratio (OR) with a two-sided 95% confidence interval. The overall two-sided type I error will be controlled at 0.05 according to the prespecified interim-analysis alpha-spending procedure.

Prespecified Covariates for Supportive Adjusted Analysis

The following baseline covariates, all measured prior to randomization, will be included in a prespecified supportive adjusted analysis:

- Age (years, continuous)
- Baseline NIHSS score (continuous)
- Baseline mRS (0 vs 1–2)
- AI-predicted infarct core volume on non-contrast CT (AI-ICV, continuous, mL)
- Time from symptom onset or last-known-well to randomization (minutes, continuous)
- Occlusion location (M2 vs non-M2)
- Use of IVT (Yes vs No)

Continuous covariates will be entered using linear terms without data-driven transformation or selection.

Adjustment for Center and Randomization Stratification Factors

Randomization will use permuted blocks within center and will be stratified by:

4. Age group (≤ 70 vs > 70 years),
5. Occlusion territory (MCA vs ACA/PCA),
6. Use of intravenous thrombolysis (IVT; yes/no).

In the primary analysis, center and the original randomization stratification factors will be included as covariates in the regression model: age group (≤ 70 vs > 70 years), occlusion territory (MCA vs ACA/PCA), and IVT use (yes/no).

Handling of Missing Data

If the primary endpoint (90-day mRS) is missing, multiple imputation under a missing-at-random (MAR) assumption will be used. The imputation model will include treatment group, center, randomization stratification factors, prespecified baseline prognostic covariates, and available post-randomization variables predictive of outcome or missingness. The primary analysis will be performed across imputed datasets and combined using Rubin's rules.

Supportive, Sensitivity, Subgroup, and Exploratory Analyses

Prespecified supportive and sensitivity analyses will include:

9. An unadjusted comparison of treatment groups using logistic regression with treatment group only.
10. An adjusted analysis including the original age stratification factor (≤ 70 vs > 70) instead of continuous age.
11. A complete-case analysis of the primary endpoint.

A per-protocol analysis as defined above.

An as-treated analysis, with participants analyzed according to treatment actually received, irrespective of randomized assignment.

Prespecified subgroup analyses by IVT use (yes/no), baseline NIHSS, and stroke etiology (ICAD vs other), assessed using treatment-by-subgroup interaction terms.

An exploratory procedural analysis comparing SAIL versus ADAPT among EVT-treated patients; because technique is not randomized, this comparison will be interpreted as exploratory.

- Secondary efficacy: The secondary endpoint (ordinal mRS at 90 days) will be analyzed using a proportional odds model including treatment group and the above prespecified baseline covariates. The treatment effect will be reported as the adjusted common odds ratio with a two-sided 95% CI; interpretation will respect the prespecified hierarchical testing procedure and overall type I error control.
- **Safety:** incidence and risk differences; DSMB-defined boundaries for harm.
- **Multiplicity:** hierarchical testing (primary $\rightarrow$ mRS shift $\rightarrow$ mRS 0–1). Others exploratory.

- Interim analyses: safety-only reviews of mortality and sICH after every 100 patients recruited; one interim efficacy/futility analysis at approximately 50% recruitment. The overall two-sided type I error rate will be controlled at 0.05 using an O'Brien–Fleming alpha-spending approach; nominal significance levels at interim and final analyses will follow the prespecified alpha-spending function.

Monitoring & Governance

- Independent DSMB; blinded Clinical Events Committee; central imaging core. The DSMB will periodically review safety events, including intracranial hemorrhage and procedure-related complications, and may evaluate whether vascular tortuosity or other anatomical characteristics are associated with increased procedural risk. Based on these reviews, the DSMB may recommend continuation without modification, protocol modification, temporary suspension, or termination for safety reasons. Any modification to eligibility criteria will require a formal protocol amendment and appropriate ethics/regulatory approval before implementation.
- Site credentialing for MeVO EVT and SAIL.
- Adherence tracking (screening log, crossovers, protocol deviations).

Missing Data Handling

If primary outcome is missing, multiple imputation will be used with an imputation model including treatment group, prespecified baseline covariates, and early post-randomization outcomes. Sensitivity analyses will assess departures from the missing-at-random assumption.

Ethics & Dissemination

Conduct under the Declaration of Helsinki and ICH-GCP. Prior IRB/ethics approvals at all sites; informed consent process (patient/LAR). Trial registration prior to first patient. Results disseminated via peer-reviewed publications and conference presentations.

Timeline (indicative)

Preparation (3 mo) → Enrollment (24 mo) → 90-day follow-up (3 mo) → Analysis & manuscript (6 mo).

13. Participating sites

Up to 10 centers will be selected to participate in the trial. Each center will enroll on average 2.5 patients per month with an enrollment period of approximately 24 months, as all centers will not be active from the beginning of the trial. The total duration of the study will be approximately 30 months allowing for initiation and close-out of study sites. Center selection will be determined by the following factors: acute ischemic stroke clinical trial experience, thrombectomy case volume, and stroke triage imaging availability.

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Appendix A. Operations manual.

Endovascular procedure and SAIL technique

All endovascular procedures will be performed under local anesthesia, conscious sedation or general anesthesia at the discretion of the treating team according to the patient's clinical condition or excessive movement of the patient. Vascular access will be obtained through a standard transfemoral approach.

ADAPT will be the preferred first-line technique when the aspiration catheter (typically 0.043-inch internal diameter) can be safely and readily advanced to the proximal aspect of the clot without excessive tortuosity and with an adequate clot/catheter interaction angle (close to 180°). A maximum of two ADAPT aspiration attempts is permitted. If these conditions are not met, or if satisfactory reperfusion is not achieved after two ADAPT attempts, treatment should transition to SAIL as described below. SAIL may therefore be used as the initial technique when anatomy is unfavorable for safe distal aspiration-catheter navigation.

When the SAIL technique will be employed, a 0.017-inch or 0.021-inch microcatheter will be navigated distal to or across the thrombus to allow deployment of a stent retriever spanning the occluded segment. Fully re-sheathable stent retrievers (typically 3 mm in diameter and 20 mm in length) will be used to permit controlled re-sheathing without traction, a key component of the SAIL technique. Full deployment of the device is generally unnecessary, minimizing disruption of the vessel's native anatomy. Smaller-diameter, shorter stent retrievers are preferred to better accommodate the caliber and tortuosity of medium and distal intracranial vessels.

After stent retriever deployment, a distal access catheter (typically 0.043–0.062 inch) will be advanced as close as reasonably possible to the thrombus, and the pharmacological agent slowly infused through the catheter (over 5 minutes approximately). The drug will be administered regardless of whether antegrade flow is restored after stent retriever deployment, as the mechanical scaffolding provided by the device may facilitate drug penetration into the thrombus even in the absence of angiographically visible reperfusion.

The standard regimen consists of:

- up to 16 mL of tirofiban solution (0.05 mg/mL; total dose 0.8 mg)
 - or up to 20 mg of tPA, typically 20 ml of the prepared dilution
 - or up to 5 mg of tenecteplase (TNK), prepared according to the study pharmacy/operations manual.
- or eptifibatide (Integrilin), prepared and administered according to the protocol-specified site pharmacy/operations manual.

It is recommended to add 1-2 ml of contrast agent. The addition of contrast enables fluoroscopic visualization of the infused solution traversing the deployed stent retriever, confirming exposure along the entire length of the thrombus

Half of the prepared solution will be infused through the distal access catheter over 5–10 minutes. After administration, a gentle angiographic run through the distal access catheter may be performed to assess recanalization.

Administration of the remaining second half of the solution will be at the discretion of the treating neurointerventionalist, based on angiographic response and clinical/procedural considerations.

Following completion of the infusion, the stent retriever will be re-sheathed into the microcatheter without retrieval in its deployed configuration, thereby avoiding traction or displacement of the affected distal arterial segment.

Angiographic reperfusion following SAIL will be assessed with an angiographic run, and the post-SAIL TICl score recorded. Additional treatment, including repeated SAIL applications or conventional mechanical thrombectomy maneuvers, is discouraged.

No post-procedural maintenance infusion of tirofiban or antithrombotic drug should be administered, except in specific situations, such as suspected underlying ICAD, in which physicians fear re-occlusion.

Antithrombotic therapy will be initiated 24 hours after the procedure according to stroke etiology and institutional standard practice.

