***Zheng L et al.*, Endovascular therapy in acute ischaemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial**

Caption for supplementary material

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SUPPLEMENTAL MATERIALS

Table of Content

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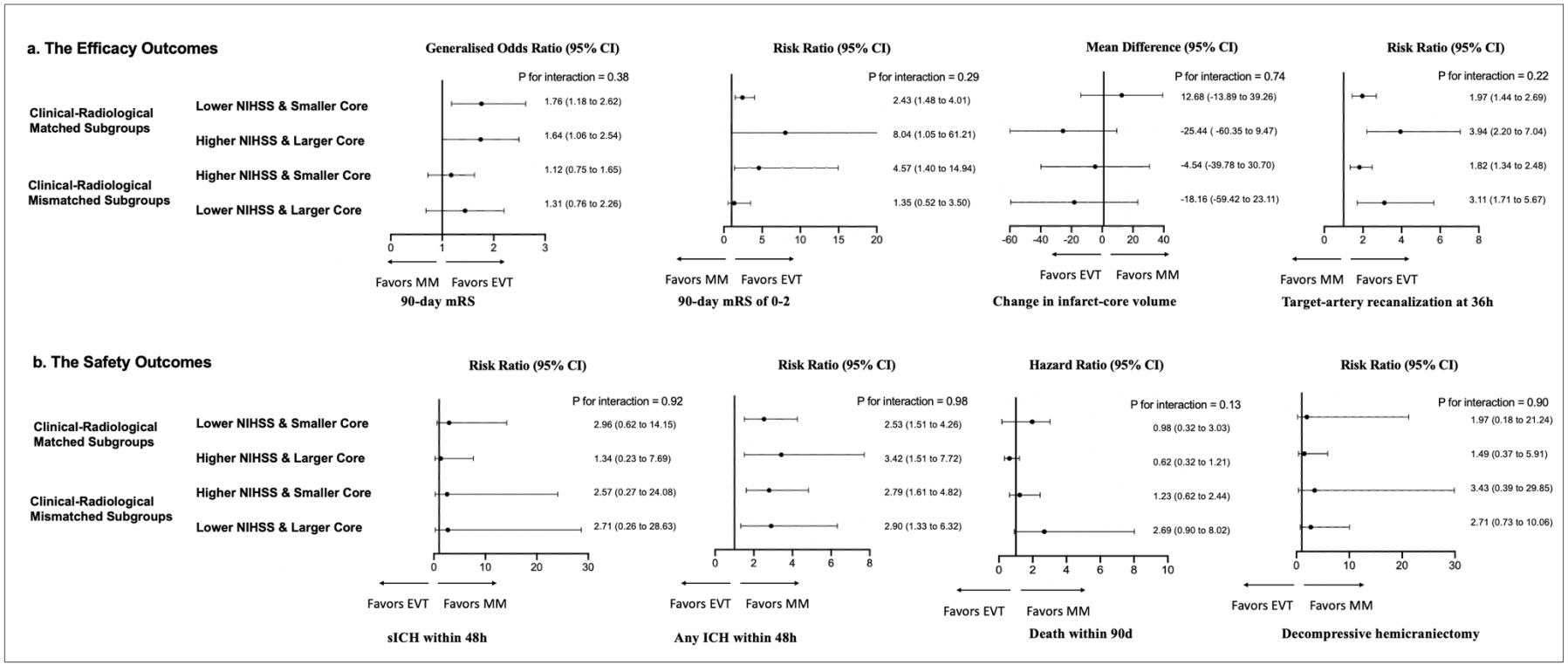

Supplemental Figure S1. Forest plots on the associations of EVT versus medical management with the efficacy (panel a) and safety outcomes (panel b) in the 4 subgroups

P for interaction of treatment arms x 4 subgroups by the clinical and radiological severities are provided in the figure.

Abbreviations: NIHSS indicates National Institutes of Health Stroke Scale; MM, medical management; EVT, endovascular therapy; mRS, modified Rankin Scale; sICH, symptomatic intracranial haemorrhage; ICH, intracranial haemorrhage.

Supplemental Table S1. Infarct locations by ASPECTS regions in the four subgroups stratified by NIHSS and infarct-core volume

ASPECTS regions	Lower NIHSS & Smaller Core (n=139)	Higher NIHSS & Larger Core (n=106)	Higher NIHSS & Smaller Core (n=130)	Lower NIHSS & Larger Core (n=80)	p value
Overall					
Internal capsule	99 (71.2)	73 (68.9)	95 (73.1)	44 (55.0)	0.04
Caudate nucleus	90 (64.8)	69 (65.1)	80 (61.5)	45 (56.3)	0.58
Lenticular nucleus	122 (87.8)	84 (79.3)	107 (82.3)	62 (77.5)	0.19
Insular ribbon	133 (95.7)	105 (99.1)	130 (100.0)	79 (98.8)	0.04
M1	79 (56.8)	80 (75.5)	75 (57.7)	58 (72.5)	0.01
M2	100 (71.9)	99 (93.4)	104 (80.0)	74 (92.5)	<0.001
M3	59 (42.5)	71 (67.0)	53 (40.8)	44 (55.0)	<0.001
M4	61 (43.9)	71 (67.0)	67 (51.5)	57 (71.3)	<0.001
M5	105 (75.5)	98 (92.5)	100 (76.9)	71 (88.8)	0.001
M6	61 (43.9)	72 (67.9)	55 (42.3)	44 (55.0)	0.001
Left hemisphere					
Internal capsule	27 (19.4)	50 (47.2)	66 (50.8)	9 (11.3)	<0.001
Caudate nucleus	26 (18.7)	49 (46.2)	56 (43.1)	9 (11.3)	<0.001
Lenticular nucleus	31 (22.3)	56 (52.8)	74 (56.9)	13 (16.3)	<0.001
Insular ribbon	34 (24.5)	70 (66.0)	88 (67.7)	16 (20.0)	<0.001
M1	15 (10.8)	57 (53.8)	49 (37.7)	15 (18.8)	<0.001
M2	22 (15.8)	67 (63.2)	69 (53.1)	15 (18.8)	<0.001
M3	14 (10.1)	50 (47.2)	31 (23.9)	8 (10.0)	<0.001
M4	13 (9.4)	48 (45.3)	45 (34.6)	12 (15.0)	<0.001
M5	25 (18.0)	66 (62.3)	71 (54.6)	16 (20.0)	<0.001
M6	15 (10.8)	48 (45.3)	35 (26.9)	10 (12.5)	<0.001
Right hemisphere					<0.001
Internal capsule	72 (51.8)	23 (21.7)	29 (22.3)	35 (43.8)	<0.001
Caudate nucleus	64 (46.0)	20 (18.9)	24 (18.5)	36 (45.0)	<0.001
Lenticular nucleus	91 (65.5)	28 (26.4)	33 (25.4)	49 (61.3)	<0.001
Insular ribbon	99 (71.2)	35 (33.0)	42 (32.3)	63 (78.8)	<0.001
M1	64 (46.0)	23 (21.7)	26 (20.0)	43 (53.8)	<0.001
M2	78 (56.1)	32 (30.2)	35 (26.9)	59 (73.8)	<0.001
M3	45 (32.4)	21 (19.8)	22 (16.9)	36 (45.0)	<0.001
M4	48 (34.5)	23 (21.7)	22 (16.9)	45 (56.3)	<0.001
M5	80 (57.6)	32 (30.2)	29 (22.3)	55 (68.8)	<0.001
M6	46 (33.1)	24 (22.6)	20 (15.4)	34 (42.5)	<0.001

Abbreviations: ASPECTS indicates Alberta Stroke Program Early Compute Tomography Score; NIHSS, National Institutes of Health Stroke Scale; M1, anterior middle cerebral artery cortex; M2, middle cerebral artery cortex lateral to the insular ribbon; M3, posterior middle cerebral artery cortex and M4, M5, M6, anterior, lateral and posterior middle cerebral artery territory immediately superior to M1, M2 and M3.

Supplemental Table S2. Efficacy and safety outcomes in the 4 subgroups, adjusting for variables unbalanced between the two treatment arms in each subgroup

	Clinical-Radiological Matched Subgroups				Clinical-Radiological Mismatched Subgroups				Adjusted p value for interaction[e]	
	Lower NIHSS & Smaller Core (n=139)		Higher NIHSS & Larger Core (n=106)		Higher NIHSS & Smaller Core (n=130)		Lower NIHSS & Larger Core (n=80)		Matched vs. Mismatched Subgroups	4 subgroups
	Adjusted treatment Effect (95% CI)[a]	p value	Adjusted treatment Effect (95% CI)[b]	p value	Adjusted treatment Effect (95% CI)[c]	p value	Adjusted treatment Effect (95% CI)[d]	p value		
Primary outcome										
90-day mRS	2.58 (1.40 to 4.77)	0.01	2.20 (1.02 to 4.75)	0.04	1.38 (0.74 to 2.58)	0.32	1.47 (0.66 to 3.29)	0.34	0.17	0.09
Secondary outcomes										
90-day mRS of 0-2	2.41 (1.46 to 3.99)	<0.001	NA	NA	4.71 (1.43 to 15.53)	0.01	1.22 (0.48 to 3.11)	0.68	0.73	0.75
Change in infarct core volume, mL	12.72 (-14.44 to 39.89)	0.36	-29.75 (-67.79 to 8.30)	0.12	-9.16 (-45.38 to 27.06)	0.62	-17.46 (-59.83 to 24.91)	0.41	0.37	0.21
Target-artery recanalization at 36h	1.93 (1.41 to 2.65)	<0.001	1.47 (1.13 to 1.92)	0.01	1.82 (1.34 to 2.49)	<0.001	2.88 (1.40 to 5.95)	0.01	0.97	0.15
Safety outcomes										
sICH within 48h	2.87 (0.59 to 14.03)	0.19	0.87 (0.15 to 5.13)	0.87	1.95 (0.20 to 19.09)	0.57	NA	NA	0.43	0.80
Any ICH within 48h	2.36 (1.38 to 4.03)	0.01	2.48 (1.09 to 5.67)	0.03	2.74 (1.58 to 4.77)	<0.001	3.30 (1.48 to 7.38)	0.01	0.50	0.77
Death within 90d	0.82 (0.26 to 2.64)	0.74	0.72 (0.34 to 1.50)	0.38	1.01 (0.49 to 2.05)	0.99	2.50 (0.83 to 7.52)	0.10	0.12	0.48
Decompressive hemicraniectomy during hospitalization	2.30 (0.21-24.68)	0.49	NA	NA	4.15 (0.48 to 35.95)	0.20	3.05 (0.81 to 11.50)	0.10	0.95	0.99

[a]Adjusted for atrial fibrillation; [b]Adjusted for ASPECTS, infarct core volume and critically hypoperfused to infarct core ratio ≥1.8 and penumbra volume ≥15 mL; [c]Adjusted for diabetes; [d]Adjusted for ASPECTS and wake-up stroke; [e]Adjusted for diabetes, atrial fibrillation, ASPECTS, infarct core volume, critically hypoperfused to infarct core ratio ≥1.8 and penumbra volume ≥15 mL and wake-up stroke.

Abbreviations: NIHSS indicates National Institutes of Health Stroke Scale; CI, confidence interval; mRS, modified Rankin Scale; sICH, symptomatic intracranial haemorrhage; ICH, intracranial haemorrhage; ASPECTS, Alberta Stroke Program Early Compute Tomography Score.

Supplemental Table S3. Efficacy and safety outcomes in the 4 subgroups classified by a combination of NIHSS < or ≥16 and infarct core volume < or ≥50mL

	Clinical-Radiological Matched Subgroups								Clinical-Radiological Mismatched Subgroups								p value for interaction	
	NIHSS <16 & core volume <70mL (n=98)				NIHSS ≥16 & core volume ≥70mL (n=148)				NIHSS ≥16 & core volume <70mL (n=88)				NIHSS <16 & core volume ≥70mL (n=121)				Matched vs. Mismatched Subgroups	4 subgroups
	MM (n=47)	EVT (n=51)	Treatment Effect (95% CI)	p	MM (n=68)	EVT (n=80)	Treatment Effect (95% CI)	p	MM (n=42)	EVT (n=46)	Treatment Effect (95% CI)	p	MM (n=68)	EVT (n=53)	Treatment Effect (95% CI)	p		
Primary outcome																		
90-day mRS	4 (3-5)	2 (2-4)	3.16 (1.52-6.56)	0.01	5 (4-6)	4 (3-6)	1.73 (0.97-3.10)	0.06	4 (3-6)	4 (3-6)	1.28 (0.61-2.70)	0.51	4 (3-5)	3 (2-4)	1.48 (0.78-2.80)	0.23	0.17	0.31
Secondary outcomes																		
90-day mRS of 0-2	9 (19.2)	29 (56.9)	2.97 (1.57-5.60)	<0.001	3 (4.4)	15 (18.8)	4.25 (1.28-14.06)	0.01	1 (2.4)	10 (21.7)	9.13 (1.22-68.32)	0.01	13 (19.1)	15 (28.3)	1.48 (0.77-2.84)	0.24	0.22	0.14
Change in infarct core volume, mL	58.9 (28.1-112.9)	47.5 (10.9-111.4)	2.74 (-28.33-33.82)	0.86	109.6 (57.0-170.7)	79.3 (27.9-170.7)	-8.83 (-42.5-24.9)	0.61	100.0 (29.9-165.7)	51.2 (32.0-132.6)	-24.11 (-59.18-10.96)	0.18	87.7 (43.3-151.7)	86.3 (37.2-134.0)	-0.38 (-33.1-32.3)	0.98	0.66	0.87
Target-artery recanalization at 36h	16 (40.0)	38 (80.9)	2.02 (1.35-3.03)	<0.001	17 (31.5)	57 (89.1)	2.83 (1.89-4.23)	<0.001	15 (45.5)	38 (88.4)	1.94 (1.32-2.87)	<0.001	19 (33.3)	36 (83.7)	2.51 (1.70-3.71)	<0.001	0.88	0.53
Safety outcomes																		
sICH within 48h	1 (2.1)	4 (7.8)	3.69 (0.43-31.81)	0.20	3 (4.4)	4 (5.0)	1.13 (0.26-4.89)	0.87	0 (0.0)	2 (4.4)	4.57 (0.23-92.62)	0.17	2 (2.9)	4 (7.6)	2.57 (0.49-13.5)	0.25	0.53	0.81
Any ICH within 48h	9 (19.2)	25 (49.0)	2.56 (1.34-4.91)	0.01	10 (14.7)	39 (48.8)	3.32 (1.79-6.13)	<0.001	8 (19.1)	23 (50.0)	2.63 (1.32-5.22)	0.01	12 (17.7)	26 (49.1)	2.78 (1.55-4.98)	<0.001	0.84	0.96
Death within 90d	5 (10.6)	3 (5.9)	0.53 (0.13-2.22)	0.39	23 (33.8)	21 (26.3)	0.73 (0.41-1.32)	0.30	11 (26.2)	14 (30.4)	1.17 (0.53-2.58)	0.70	6 (8.8)	12 (22.6)	2.77 (1.04-7.37)	0.04	0.03	0.10
Decompressive hemicraniectomy during hospitalization	1 (2.1)	1 (2.0)	0.92 (0.06-14.32)	0.95	4 (5.9)	8 (10.0)	1.70 (0.54-5.40)	0.36	0 (0.0)	1 (2.2)	2.74 (0.11-65.59)	0.34	3 (4.4)	7 (13.2)	2.99 (0.81-11.03)	0.08	0.46	0.85

Abbreviations: NIHSS indicates National Institutes of Health Stroke Scale; MM, medical management; EVT, endovascular therapy; CI, confidence interval; mRS, modified Rankin Scale; sICH, symptomatic intracranial haemorrhage; ICH, intracranial haemorrhage.

Protocol and Statistical Analysis Plan

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Study of Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a LargE InfarCT Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial.

Study of Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a LargE InfarCT Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial (ANGEL-ASPECT)

Protocol

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Protocol Version 6.0

Date: July 23, 2020

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Protocol Signature Page

I have read this protocol and agree to adhere to the requirements.

By signing this document we confirm that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

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Clinical Site

_____ _____

Site Principal Investigator Signature Date

ANGEL-ASPECT Protocol Synopsis

Official Title		Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial
Acronym		ANGEL-ASPECT
Sponsor		Beijing Tiantan Hospital, Capital Medical University
Study Centers		~50 centers in China
Statement of Hypothesis		Best medical management (BMM) combined with endovascular Therapy (EVT) might be superior to BMM alone in acute anterior circulation large vessel occlusive (LVO) patients with a large infarct core.
Study Objectives	**Primary objective**	To evaluate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have improved neurological functional outcomes when treated with BMM plus EVT compared to BMM alone.
	Secondary objective	To assess if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have increased risk of symptomatic intracranial hemorrhage (sICH) when treated with BMM plus EVT compared to BMM alone.
Study settings		Multicenter, Prospective, Randomized, Open-label, Blinded End-point (PROBE) design
Randomization		Participants will be randomized in a 1:1 ratio based on simple randomization of the central network

		randomization system to receive BMM plus EVT or BMM alone.
Sample Size		A total of 488 patients are planned to be enrolled. Interim analysis will take place when 1/2 (244 cases) and 3/4 (366 cases) have completed 3-month follow-up.
Efficacy Endpoints	**Primary Endpoint**	90 days (±7 days) modified Rankin Scale (mRS)
	Secondary Endpoints	(1) 90 days (±7 days) mRS 0-2 (2) 90 days (±7 days) mRS 0-3 (3) 36 hours (±12 hours) NIHSS 0-1 or decrease ≥10 from baseline (4) Infarct core volume change from baseline, at 7 days (±1 day) or at discharge assessed with NCCT or at 36 hours (±12 hours) assessed with MRI (5) 36 hour (±12 hours) target artery recanalization rate assessed with CTA or MRA
Safety Endpoints	**Primary Safety Endpoint**	Rate of sICH within 48 hours from randomization (Heidelberg Bleeding Classification)
	Secondary Safety Endpoints	(1) All-cause mortality within 90 days (±7 days) (2) Any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification) (3) Decompressive hemicraniectomy during hospitalization
Participants	**Inclusion Criteria**	**Center Inclusion Criteria** (1) Equipped with emergency department and neurology department for stroke patients

		(2) Equipped with stroke team operating 24/7 (3) Capable of EVT and intravenous (IV) thrombolysis for acute ischemic stroke patients **Clinical Inclusion Criteria:** (1) Age 18-80 years (2) Presenting with symptoms consistent with acute ischemic stroke (3) Pre-stroke mRS score 0-1 (4) NIHSS score 6-30 at the time of randomization (5) Randomization can be finished within 24 hours from stroke onset (stroke onset time is defined as last known well time) (6) Informed consent signed **Neuroimaging Inclusion Criteria:** (1) CTA or MRA proven occlusion of the Internal Carotid Artery (ICA) terminus or M1 segment of Middle Cerebral Artery (2) Imaging evidence of low Alberta Stroke Program Early CT Score (ASPECTS) (based on non-contrast CT) or large infarct Core (defined as rCBF <30% on CT perfusion or ADC<620 × 10^{-6} mm^2/s on MRI) fulfilling one of the following criteria: 1) ASPECTS 3–5 2) ASPECTS >5 (6-24 h) with infarct core volume 70-100 ml 3) ASPECTS <3 with infarct core volume 70-100 ml (3) Mismatch ratio on CT perfusion or MRI (Tmax>6s volume / Ischemic core volume) >1.2

	Exclusion Criteria	**Center Exclusion Criteria** (1) Centers in which the number of acute ischemic stroke cases treated with endovascular procedures are less than 20 per year; (2) Centers unable to comply with the research protocol **Clinical Exclusion Criteria** (1) Females who are pregnant, or those of childbearing potential with positive urine or serum beta Human Chorionic Gonadotropin test (2) Known severe allergy (more severe than skin rash) to contrast agents uncontrolled by medications (3) Refractory hypertension that is difficult to control by medication (defined as persistent systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg) (4) Known hemorrhagic tendency (including but not limited to): Baseline platelet count $< 100\times10^9$/L; Heparin was administered within 48 hours with aPTT≥35s; on anticoagulant therapy with warfarin and International Normalized Ratio (INR) > 1.7 (Patients with no history or suspected coagulopathy do not need to wait for laboratory results of INR or aPTT prior to enrollment) (5) Parenchymal organ surgery and biopsy were performed in the past one month (6) Any active bleeding or recent bleeding (gastrointestinal bleeding, urinary bleeding, etc.)

		in the past one month (7) Undergoing hemodialysis or peritoneal dialysis; Known severe renal insufficiency with glomerular filtration rate <30 ml/min or serum creatinine >220 mmol/L (2.5mg/dl) (8) Brain tumor (with mass effect) (9) The expected survival time is less than 1 year (such as comorbidity with malignant tumor, serious heart and lung diseases, etc.) (10) Participation in other interventional randomized clinical trials that may confound the outcome assessment of the trial (11) Other circumstances that the investigator considers inappropriate for participation in the trial or that may pose significant risk to the patient (such as inability to understand and/or follow the study procedures and/or follow up due to mental disorders, cognitive or emotional disorders) **Neuroimaging Exclusion Criteria** (1) Midline shift or herniation, mass effect with effacement of the ventricles (2) Evidence of acute intracranial hemorrhage (3) Acute bilateral strokes or multiple intracranial vessel occlusion
Treatment Allocation	**Study Arm**	BMM plus EVT
	Control Arm	BMM alone

Follow-up schedule	Study visits will take place on the day of randomization, at 36 hours (± 12 hours), 7 days (±1 day)/at discharge whichever is earlier, 30 days (±3 days), 90 days (±7 days) and 12 months (± 14 days).
Subgroup analysis	Subgroup analysis will be performed based on the following variables: (1) Age (< 70 years vs. ≥70 years) (2) Last known well to randomization time (< 6 h vs. ≥ 6 h) (3) Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16) (4) IV thrombolysis (5) Occlusion site (intracranial ICA vs. M1 segment) (6) ASPECTS score (< 3 vs. ≥3 points) (7) Infarct core volume (< 70ml vs. ≥70ml) (8) Etiological subtype of stroke (cardiac embolism vs. large artery atherosclerosis)
Study duration	August 2020 to October 2022 (enrolment completed October 2021)

Abbreviations

ADC	Apparent Diffusion Coefficient
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
ASPECTS	Alberta Stroke Program Early CT Score
BMM	Best Medical Management
CEC	Clinical Events Adjudication Committee
CI	Confidence Interval
CRA	Clinical Research Associate
CRC	Clinical research coordinator
CRF	Case Report Form
CSA	Chinese Stroke Association
CT	Computer Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion Imaging
DAWN	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
DICOM	Digital Imaging and Communications in Medicine
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
DWI	Diffusion Weighted Imaging
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	EuroQoL 5-Dimensions 5-Level questionnaire
eTICI	Expanded Thrombolysis in Cerebral Infarction
EVT	Endovascular Therapy
FAS	Full Analysis Set
FLAIR	FLuid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GRE	Gradient Echo
GSR-ET	German Stroke Registry – Endovascular Treatment
ICA	Internal Carotid Artery
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
INR	International Normalized Ratio

IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
LICV	Large Infarct Core Volume
LLC	Limited Liability Company
LVO	Large Vessel Occlusive
MCA	Middle Cerebral Artery
MM	Medical Management
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCCT	Non-contrast computed tomography
NCSS	Number Cruncher Statistical System
NIHSS	National Institute of Health stroke scale
NMPA	National Medical Products Administration
OR	Odd Ratio
PASS	Power Analysis and Sample Size
PPS	Per Protocol Set
PROBE	Prospective, Randomized, Open-label, Blinded End-point
PWI	perfusion weighted imaging
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SELECT	Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke
sICH	Symptomatic intracranial hemorrhage
THRACE	Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke
TICI	Thrombolysis In Cerebral Infarction
T-NICE	Tiantan Neuroimaging Center of Excellence
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

1. Background

Large clinical trials on early and late window stroke patients have helped to establish the indications for endovascular treatment (EVT) of acute ischemic stroke (AIS) patients with large vessel occlusion (LVO).[1,2] The neuroimaging criteria upon which the trials have shown benefit includes patients presenting with Alberta Stroke Program Early CT Scores (ASPECTS) score ≥ 6 within 6 hours,[3-7] and patients meeting DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial imaging criteria at 6-24 and 6-16 hours from time last seen well, respectively.[8,9] Since then, many clinical trials have undergone an expansion of the indications of EVT for AIS patients with LVO. Whether patients with large infarct core volume (LICV) are suitable for EVT is one of the unanswered questions.

1.1 The rational of EVT for large infarct core volume

Several retrospective studies, prospective studies, and meta-analyses suggest that patients with LICV may benefit from EVT. The Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE) trial was one of the early randomized trials to enroll patients with ASPECTS<6.[10] A subgroup analysis of the THRACE trial showed that among 53 subjects with a diffusion-weighted imaging (DWI) volume of >70 ml, 12 (22.6%) patients of the EVT group had good clinical outcomes (mRS ≤ 2 at 90 days).[11] The prospective German Stroke Registry – Endovascular Treatment (GSR-ET) also showed that 22% of 152 thrombectomy patients with ASPECTS <6 achieved independence with mRS 0-2 at 90 days.[12] The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration pooled their data from six early window trials. It showed a benefit of EVT over control was observed in patients with ASPECTS 0–4 or DWI-determined infarct core volume ≥ 70 ml. Functional improvement (mRS 0-2 at 90 days)

rates in the EVT group compared with the control group were 25% vs. 14% and 30% vs.20%, respectively.[13,14]

In the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) trial, the prespecified secondary analysis of 105 patients (of whom 62 received EVT) with ASPECTS ≤ 5 or CTP-determined ischemic core volume ≥ 50 ml showed that functional independence was achieved in 31% in the EVT group vs. 14% in the control group.[15] Incidence rates of death, neurologic decline, and symptomatic intracerebral hemorrhage (sICH) were similar in both groups. In addition, EVT was associated with less infarct growth (44 vs. 98 mL; p=0.006) and smaller final infarct volume (97 vs. 190 mL; p=0.001) compared to medical management (MM).

One meta-analysis including 17 studies and 1378 patients with ASPECTS 0–6 (1194 EVT, 184 MT) found that mRS 0–2 was achieved in 30.1% of cases after EVT and in 3.2% after MM (OR 4.76, p=0.01).[16] The marked lower rate in the MM group compared to previous RCTs (HERMES: 14%, SELECT: 14%) is likely due to the imbalance of baseline characteristics of the patients in these retrospective studies. For example, patients in the MM group were older (75 years vs 68.7 years), had higher NIHSS scores (19 vs. 18), lower rate of intravenous (IV) thrombolysis (47.8% vs. 56.8%) and longer symptom onset to admission time (130 min vs. 115 min). Successful recanalization (Thrombolysis in Cerebral Infarction (TICI) grade 2b–3) led to higher odds of mRS 0–2 than unsuccessful reperfusion (OR 5.2, p=0.001). Another pooled random-effect meta-analysis, including 12 studies of large core patients (ASPECTS <6 or ischemic core volume ≥ 50 ml), demonstrated higher functional independence (mRS 0–2) rates with EVT (25% vs 7%; pooled OR: 4.39, 95% CI: 2.53 to 7.64), and decreased mortality (23% vs. 33%; pooled OR: 0.53, 95% CI: 0.40 to 0.71).[17]

In a matched case-control study of 56 patients (28 pairs) with ICA, M1 and M2 occlusion and CTP-determined infarct core > 50mL, EVT led to higher rates of functional independence (90-day mRS 0-2, 25% vs 0%; p=0.04), and smaller final infarct volumes (87 vs 242 mL; p <0.001).[18] One control (4%) and two treatment patients (7%) developed a parenchymal hematoma type 2 (p>0.99). The rates of

hemicraniectomy (7% vs 21%; p=0.10) and 90-day mortality (29% vs 48%; p=0.75) were lower in the EVT arm. Sensitivity analysis for patients with a baseline infarct core volume greater than 70 mL (12 pairs) revealed a significant reduction in final infarct volumes (110 vs. 319 mL; p<0.001) but only a nonsignificant improvement in the overall distribution of mRS scores favoring the treatment group (p=0.18).

Interestingly, one observational cohort study included a consecutive sample of 170 patients with anterior circulation stroke and initial ASPECTS ≤ 5 (99 patients in the EVT group, 71 patients in the MM group). The study showed that clinical outcome after failed or incomplete EVT (TICI 0–2b) was significantly better compared to patients with MM only (median mRS 5, interquartile range 4–6 vs. 5–6, p=0.03). Failed EVT (TICI 0–2a) was not associated with a worse outcome than MM.[19]

1.2 Image modality to identify large infarct core volume

Generally speaking, there are two imaging evaluation methods for large infarct core, one is a semi-quantitative evaluation based on CT/MRI-ASPECTS, and the other is a quantitative evaluation based on CTP/MRI with the aid of automated artificial intelligence software. ASPECTS is a widely accepted tool used to assess infarct volume. In general, ASPECTS < 6 is regarded as a "large core infarct." However, multiple studies have shown low interrater agreement with ASPECTS.[20,21] An inaccurate ASPECTS can misclassify patients between the EVT and control groups, weakening any trial conclusions. Quantitative determination of infarct core volume using CTP/MRI could compensate for poor inter-rater reliability in the interpretation of ASPECTS.

Notably, the correlation between the CTP/MRI-determined infarct core volume and ASPECTS is not well established. Therefore, the optimal imaging modality for evaluating patients with LICV in clinical trials remains to be explored. The subgroup analysis in a meta-analysis comparing outcomes between these two imaging modalities did not find significant heterogeneity in the results when LICV was defined based on ASPECTS or ischemic core volume of CTP.[17] While one study[22] found a good

correlation between ASPECTS and CTP/MRI volume, others found them to be discordant.[15,17,23] To expedite enrollment, this study allowed the use of non-contrast CT (NCCT)-ASPECTS and/or CTP/MRI imaging modalities to screen patients with LICV.

1.3 ASPECTS and infarct core volume selection

A recent meta-analysis of 17 studies and 1378 patients reported functional independence, or a mRS 0-2, was achieved by 37.7%, 33.3%, 22.1%, and 17.1% of patients with ASPECTS 6, 5, 4 and 0-4 respectively.[16] The studies by Mourand et al.[24] and Inoue et al.[25] showed favorable outcomes in between 16% and 20% of patients with ASPECTS 0–3 after EVT. Another meta-analysis showed that patients presenting with an ASPECTS 0-2 had better outcomes with MM instead of EVT.[13] The benefit of EVT declined with decreasing in ASPECTS, especially with ASPECTS < 3, because the infarct core volume was very large and there was less salvageable brain tissue, which might make EVT ineffective.[13,26,27] Therefore, this study limited the ASPECTS of enrolled patients to 3-5.

There is some debate about whether “large core” should be defined as 50ml vs. 70ml on CTP. In ANGEL-ASPECT, the infarct core volume > 70 ml was defined as LICV. Similar to patients with ASPECTS 0-2, patients with excessive infarct core volume may also be less likely to benefit from EVT. Previous studies showed a lack of benefit if CTP-determined core volume exceeded 100 ml and 150 ml.[14,15] Therefore, when patients were enrolled only based on the infarct core volume as assessed by CTP/MRI, this study limited the infarct core volume to 70 ml-100 ml.

1.4 EVT time window for large infarct core volume

Patients in the hyperacute phase of stroke may exhibit an increased ASPECTS lesion growth from imaging to recanalization, suggesting a benefit of faster recanalization in these patients.[28] A meta-analysis by Cagnazzo et al. demonstrated that a shorter time from onset to reperfusion was associated with a higher probability of

functional independence after EVT in patients with ASPECTS 0–6.[16] The SELECT trial found that patients with LICV had a gradual decline in functional outcomes with prolonged treatment time, with a lower likelihood of benefit from EVT after 12 hours from symptom onset or time last seen well.[15] This suggested that for LICV patients, earlier EVT may be more beneficial. However, a recent meta-analysis found that patients with LICV did not show a significant difference in outcomes among studies reporting <6 hours, <12 hours, and <24 hours for stroke to EVT time windows.[17] This may be because most LICV patients presented in the early time window, reducing the power to detect a difference between early and late windows. The reason may also be that the efficacy of MM declines over time, thus preserving the efficacy of EVT. In this context, it is important to study whether EVT also benefits patients with LICV in the late time window, therefore the time window of ANGEL-ASPECT is 0-24 hours.

1.5 ANGEL-ASPECT Trial design

The ANGEL-ASPECT trial is a PROBE study initiated by researchers to explore the effectiveness and safety of EVT in patients with anterior circulation large vessel occlusion stroke with ASPECTS 3-5 or infarction core volume 70-100ml within 24 hours of symptom onset. The ANGEL-ASPECT trial allows multiple imaging modalities to screen for LICV patients, but at the same time imposes limitations on the range of ASEPCTS or infarct core volume. The purpose was to reduce the risk of EVT while enrolling as many LICV patients as possible. The primary image inclusion criteria of ANGEL-ASPECT was NCCT-ASPECTS 3-5, and the infarct core volume of 70 ml-100 ml was used as auxiliary inclusion criteria. Briefly, the inclusion criteria for LICV are: (1) If NCCT-ASPECTS is 3-5 and presentation is within 24 hours of onset, patients are enrolled without limitation of infarct core volume. (2) For NCCT-ASPECTS 0-2 and core infarction volume 70 ml-100 ml, patients are enrolled. (3) If NCCT-ASPECTS is >5 and between 6 to 24 hours from symptom onset, only patients with infarct core volume 70 ml-100 ml are enrolled.

Subgroup analysis will focus on age, LKW to randomization time, NIHSS score,

IV thrombolysis, occlusion site, ASPECTS, infarct core volume, and stroke etiology.

ANGEL-ASPECT is the only randomized controlled trial conducted in China for LICV patients thus far. The results of this trial will clarify whether EVT is effective and safe in Chinese patients with LICV.

2. Study objective

2.1 Primary objective

To evaluate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have improved neurological functional outcomes when treated with BMM plus EVT compared to BMM alone.

2.2 Secondary objective

To assess if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have an increased risk of sICH when treated with BMM plus EVT compared to BMM alone.

3. Study design

3.1 Study design

Multicenter, Prospective, Randomized, Open-label, Blinded End-point (PROBE) trial design (Figure 1).

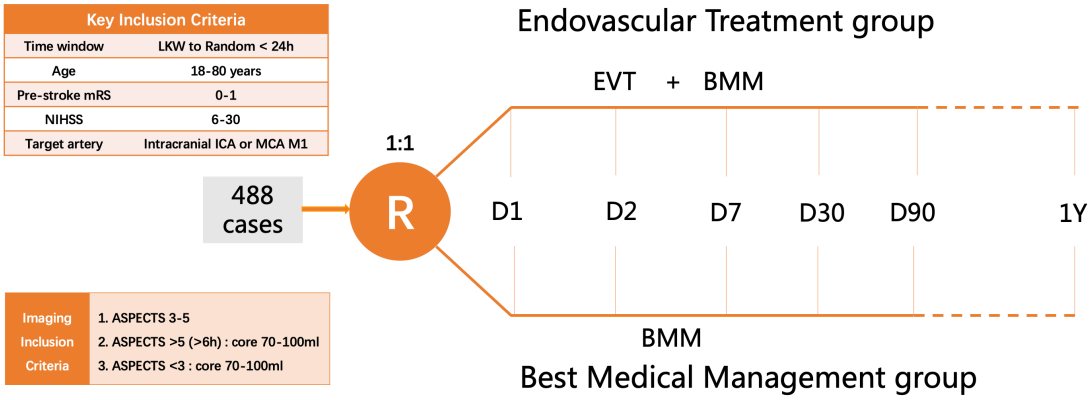

Figure 1. Study design: Randomization Algorithm

3.2 Randomization

The random code will be generated by a central network randomization system with 24h real-time randomization online based on the simple randomization method. The researcher in each center will obtain the random code from the central network randomization system according to the enrollment order. Patients who meet the inclusion criteria and in whom written informed consent can be obtained, will be randomly assigned to the following treatment groups in a 1:1 ratio:

- BMM plus EVT group: patients will receive EVT with stent retriever or contact aspiration as first-line devices for thrombectomy plus BMM;
- BMM group: Patients will receive BMM alone.

3.3 Follow-up schedule

(1) Face-to-face visit: day of randomization, 36 hours (±12 hours), 7 days (±1 day) /at discharge whichever is earlier

(2) Telephone visit: 30 days (±3 days), 90 days (±7 days), and 12 months ±14 days

3.4 Blind design

(1) Only the patient and the treating physician are aware of the randomization

information, and the evaluation of information at baseline and in-hospital visits that relate to the study endpoints should be evaluated by an investigator who is not aware of the patient groups and actual treatment.

(2) The primary endpoint visits are standardized visits conducted by trained third party personnel who are not aware of the patient's randomization assignment and their treatment. All follow-up calls will be recorded, and a follow-up report will be formed.

(3) All imaging data related to the study will be collected for centralized interpretation. The images at each visit site will be interpreted independently by a core lab, and the readers will be unaware about the baseline, treatment received (except EVT angiography images), and prognosis.

4. Participant selection

4.1 Inclusion Criteria

4.1.1 Center Inclusion Criteria

(1) Equipped with an emergency department and neurology department for stroke patients

(2) Equipped with a stroke team operating on 24/7

(3) Capable of endovascular therapy and IV thrombolysis for acute ischemic stroke patients

4.1.2 Clinical Inclusion Criteria

(1) 18 to 80 years of age

(2) Presenting with symptoms consistent with an acute ischemic stroke

(3) Pre-stroke mRS score 0-1

(4) NIHSS score 6-30 at the time of randomization

(5) Randomization can be finished within 24 hours of stroke onset (stroke onset time is defined as last known well time)

(6) Informed consent signed by the patient or legally authorized representative

4.1.3 Neuroimaging Inclusion Criteria

(1) CTA or MRA proven occlusion of the Internal Carotid Artery (ICA) terminus or M1 segment of the Middle Cerebral Artery (MCA)

(2) Imaging evidence of low ASPECTS (based on NCCT) or large infarct Core (defined as rCBF <30% on CT perfusion or ADC<620 $\times 10^{-6}$ mm^2/s on MRI) fulfill one of the following criteria:

   1) ASPECTS 3-5
   2) ASPECTS >5 (6h-24 h) with infarct core volume 70-100 ml
   3) ASPECTS <3 with infarct core volume 70-100 ml

(3) Mismatch ratio on CT perfusion or MRI (Tmax>6s volume / Ischemic core volume) >1.2

4.2 Exclusion Criteria

4.2.1 Center Exclusion Criteria

(1) Centers in which the number of acute ischemic stroke cases treated with endovascular procedures are less than 20

(2) Incapable of complying with the protocol to proceed with the research

4.2.2 Clinical Exclusion Criteria

(1) Females who are pregnant, or those of childbearing potential with positive urine or serum beta Human Chorionic Gonadotropin test

(2) Known severe allergy (more than a rash) to contrast media uncontrolled by medication

(3) Refractory hypertension that is difficult to be controlled by medication (defined as persistent systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)

(4) Known hemorrhagic tendency (including but not limited to): Baseline platelet count < 100×10^9/L; Heparin was administered within 48 hours with aPTT≥35s; on anticoagulant therapy with warfarin and International Normalized Ratio (INR) > 1.7 (Patients with no history or suspected coagulopathy do not need to wait for laboratory results of INR or

aPTT prior to enrollment)

(5) Parenchymal organ surgery and biopsy were performed in the past one month

(6) Any active bleeding or recent bleeding (gastrointestinal bleeding, urinary bleeding, etc.) in the past one month

(7) Undergoing hemodialysis or peritoneal dialysis; Known severe renal insufficiency with glomerular filtration rate <30ml/min or serum creatinine >220mmol/L (2.5mg/dl)

(8) Brain tumor (with mass effect)

(9) The expected survival time is less than 1 year (such as comorbidity with malignant tumor, advanced heart or lung disease, etc.)

(10) Participation in another interventional randomized clinical trial that may confound outcome assessment of the study

(11) Other circumstances that the investigator considers inappropriate for participation in the study or that may pose significant risks to patients (such as inability to understand and/or follow the study procedures and/or follow up due to mental disorders, cognitive or emotional disorders)

4.2.3 Neuroimaging Exclusion Criteria

(1) Midline shift or herniation, mass effect with effacement of the ventricles

(2) Evidence of acute intracranial hemorrhage

(3) Acute bilateral strokes or multiple intracranial vessels occlusions

5. Imaging protocol

5.1 Baseline imaging

All researchers will be trained in the course of the imaging protocol, the use of RAPID software, participate in the network training, simulation test and examination of NCCT-ASPECTS before enrollment. The ASPECTS training and test are conducted through the online training system of the trial website (http://angel-aspect.org). Those

who pass the exam (accuracy rate more than 80%) will obtain the ASPECTS assessment qualification certificate and be qualified for imaging assessment. During imaging screening, researchers in the sub-center with imaging evaluation qualifications and two trained neuroradiologists from the trial team will conduct real-time online image evaluation of ASPECTS, occlusion site, infarct core volume to ensure the accuracy of the imaging assessment (Figure 2).

(1) **ASPECTS:** All patients presenting within 24h of symptom onset will undergo a plain CT scan. After the preliminary screening of ASPECTS by trained clinicians in research centers, two dedicated clinicians from the trial team will conduct real-time online evaluation. When the ASPECT score reaches a consensus that is between 3 to 5, the patient is suitable for enrollment. NCCT-ASPECTS will be manually determined independently before RAPID ASPECTS® (version 5.0.4, iSchemaView, CA, USA) assessment.

(2) **Infarct core volume:** The infarct core volume will be automatically evaluated by iSchemaView automated RAPID® software (version 5.0.4, iSchemaView, CA, USA), and the infarction core volume is defined as rCBF<30% based on CTP or ADC<620 $\times 10^{-6}$ mm^2/s based on MRI. For patients who present with NCCT-ASPECTS 0-2 within 6 hours from symptom onset, if the infarct core volume is between 70ml and 100ml, then the patient is eligible for enrollment. If the infarct core volume is between 70ml and 100ml in an extended time window (6-24 hours) of stroke onset, the patient is also suitable for inclusion regardless of ASPECTS.

(3) **Target arterial occlusion:** The site of arterial occlusion will be determined by CTA or MRA. Occlusion of the ICA or M1 segment of the MCA is suitable for enrollment. Patients with ipsilateral extracranial internal carotid artery occlusion or stenosis with the above artery occlusion will also be included in this trial. As a tandem lesion can be difficult to distinguish on CTA or MRA, patients with tandem lesion in the EVT group will be confirmed during angiography.

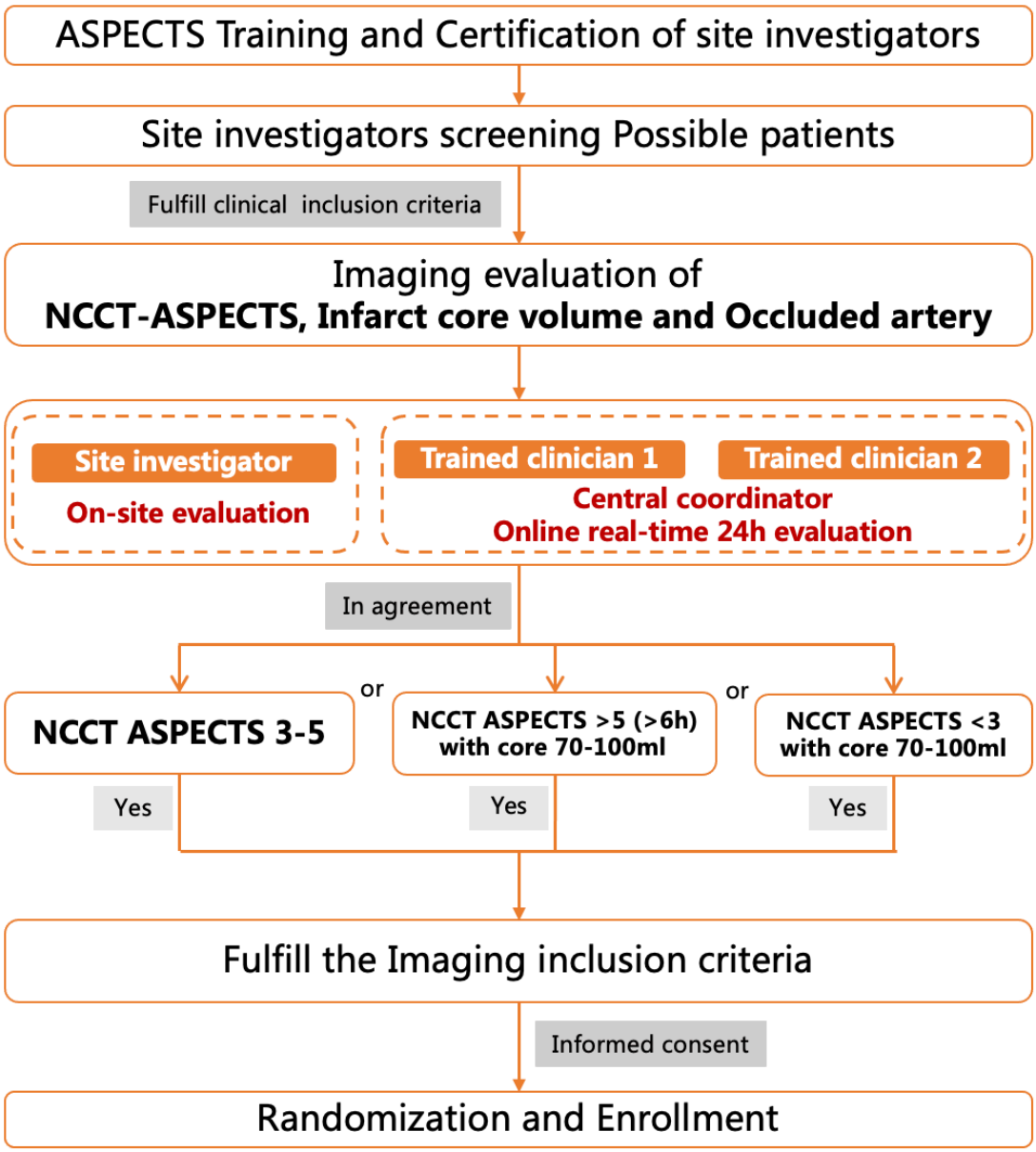

Figure 2. Imaging evaluation workflow

5.2 Intraoperative and follow-up imaging:

(1) **Intraoperative imaging:** In the EVT group, preoperative DSA will be required to determine the site of vascular occlusion and eTICI score,[29] and postoperative angiography will be required to evaluate the eTICI score. It is recommended to conduct NCCT or cone-beam CT immediately after EVT to exclude bleeding.

(2) **Imaging evaluation of hemorrhage:** The NCCT scan 36 hours (±12 hours) after

randomization will be utilized as the main criterion to adjudicate hemorrhage, and the Heidelberg Bleeding Classification will be used for hemorrhage classification.[30]

(3) **Vascular imaging follow-up:** Vascular imaging (CTA/MRA) will be conducted within 36 hours (±12 hours) h after randomization to determine vascular patency.[31]

(4) **Evaluation of postoperative infarct volume:** The infarct core volume will be determined at 7 days (±1 day) or at discharge as assessed with NCCT or at 36 hours (±12 hours) assessed with MRI, and the infarct core volume will be determined manually by the imaging core lab using validated automated software.[32]

5.3 Imaging core lab

The Tiantan Neuroimaging Center of Excellence (T-NICE) is the imaging core lab of this trial. During the period from patient presentation to discharge, all imaging data (CT, CTA, CTP, MRI, MRA, PWI, DSA) will be collected by CRO in DICOM format. All images will be quality controlled, rendered anonymous and sent to T-NICE for central adjudication. The final results will be reviewed and confirmed by the imaging assessment committee, and then input into the database.

6. Treatments

Patients meeting the eligibility criteria and signing the informed consent will be randomized. Patients randomized to the interventional arm will receive BMM plus EVT. Artery puncture should be performed within 1 hour of randomization. Patients randomized to the medical arm will receive BMM.

6.1 Endovascular Therapy (EVT)

When the patient's condition permits, local anesthesia is the first choice for rapid initiation of puncture and endovascular therapy. Conscious sedation can be used, and intubation can be considered for patients at high risk of airway collapse. If the patient is expected to have poor intraprocedure cooperation, is at high risk of using sedation or

if there are other airway conditions due to the patient's illness, general anesthesia should be used. Return to the Neuro-Intensive Care Unit (NICU) with intubation or not will be determined according to the procedural results.

Systemic heparinization is not recommended for preoperative and intraoperative treatment. Femoral artery is suggested for arterial puncture, and a long sheath, guiding catheter or balloon guide catheter can be used. Stent retriever (Solitaire, EMBOTRAP, Reco, Captor or other first-line stent retriever systems) and/or contact aspiration (Penumbra aspiration system or other first-line aspiration system) are recommended as the first-line choice for thrombectomy. If successful reperfusion (eTICI 2b50-3) is not achieved after routine thrombectomy, other techniques are allowed for rescue treatment, including replacement of thrombectomy technique, replacement of thrombectomy device, intra-arterial thrombolysis, balloon angioplasty or stent implantation, etc. The need for rescue treatment is defined (including, but not limited to, a decision made by the investigator based on intraprocedure conditions) as follows: three thrombectomy passes with the same device (stent retriever or aspiration catheter) without successful recanalization; Target vessels were successfully recanalized and reoccluded; Target vessel dissection or stenosis ≥70%, with any degree of antegrade blood flow disturbance; New intraluminal/stent thrombosis resulting in a decrease of eTICI score.

All the above procedures should be performed using devices approved by the National Medical Products Administration (NMPA) and should be performed in accordance with the approved intended use and operating instructions.

6.2 Best Medical Management (BMM)

All enrolled patients should receive BMM in accordance with the recommendation of the “Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders” by the Chinese Stroke Association (CSA).[33] This includes IV thrombolysis therapy for patients meeting the guideline. Patients who meet criteria should receive IV thrombolysis therapy according to the guidelines. Patients who plan to undergo or are undergoing IV thrombolysis therapy can decide whether to terminate

IV thrombolysis therapy in advance according to the investigator's judgment after enrollment. Patients who had completed IV thrombolysis prior to randomization are also eligible for inclusion in this study. All patients will be required to record the name, dosage and time of IV thrombolysis medication in detail. Antiplatelet agents are not recommended within 24 hours after IV thrombolysis unless the patient has undergone balloon dilatation or stent implantation, at which time the antithrombotic strategy is determined by the investigator. Based on the time window and infarct core volume for ANGEL-ASPECT, it is anticipated that most patients enrolled in ANGEL-ASPECT will not have received IV thrombolysis prior to randomization. Non-IV thrombolysis patients will be treated with aspirin, unless an indication for early anticoagulation is present.

7. Study endpoints

7.1 Primary efficacy endpoint

90 days (±7 days) modified Rankin Scale (mRS)

7.2 Secondary efficacy endpoint

(1) 90 days (±7 days) mRS 0-2
(2) 90 days (±7 days) mRS 0-3
(3) 36 hours (±12 hours) NIHSS 0-1 or decrease ≥10 from baseline
(4) Infarct core volume change from baseline, at 7 days (±1 day) or at discharge assessed with NCCT or at 36 hours (±12 hours) assessed with MRI
(5) 36 hour (±12 hours) target artery recanalization rate assessed with CTA or MRA

7.3 Primary safety endpoint

Rate of sICH within 48 hours from randomization (Heidelberg Bleeding Classification, Appendix 5)

7.4 Secondary safety endpoint

(1) All-cause mortality within 90 days (±7 days)
(2) Any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification)
(3) Decompressive hemicraniectomy during hospitalization

8. Data collection and Study procedure

Investigator(s) should keep a record, the eligibility Case Report Form (CRF), of subjects who enter pre-study screening. The sub-center number must be indicated. The screening table will be used to analyze and determine whether the enrolled patients in different study sites are representative. Referring to the procedure manual and data collection guidelines, investigators should guarantee the input of CRF is precise, complete and timely, and answer the queries in time. Brain imaging which includes: CT, CTA, CTP, MRI (T1+T2+DWI+FLAIR+ADC+GRE-T2*/SWI+MRA±PWI) and DSA will be collected as DICOM format. Laboratory results will be collected via photocopies of the reports.

8.1 Screening and Inclusion

- Basic data collection: hospital name, name of patient identification, age, sex, allergy to contrast agent.
- History of present event: time of onset (time of last known well), time of arrival at the hospital, type of onset, IV thrombolysis after onset (initial time, name and dose of the drug).
- Medical history and medication before onset

  Medical history (smoking, drinking, hypertension, diabetes, dyslipidemia, cardiac arrhythmia, valvular heart disease, cardiac insufficiency, coronary atherosclerotic heart disease, peripheral arterial disease, TIA,

cerebral infarction, cerebral hemorrhage, intracranial tumors), pre-stroke mRS;

Combination therapy: Antiplatelet drugs (aspirin, clopidogrel, cilostazol, prasugrel, ticagrelor, ticlopidine, etc.), anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, argatroban, etc.), statins (atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, fluvastatin, etc.).

- Physical examination

Height and weight, blood pressure, pulse, neurological evaluation (NIHSS and Glasgow scale), 12-lead electrocardiogram (ECG) .

- Emergency laboratory examinations

Emergency blood routine, emergency renal function, emergency liver function (transaminase), emergency coagulation, random blood glucose, etc.

- Imaging

A head CT is required to rule out hemorrhage and perform ASPECTS evaluation; a CTA or MRA is essential to confirm the site of artery occlusion; a CTP or MRI is required to calculate the infarct core volume

- All participants or his/her authorized representative need to sign a written informed consent form
- Included subjects will be randomized

8.2 Data to be collected during procedure

- General anesthesia with intubation or conscious sedation with local anesthesia at start of procedure

- Procedure times: groin puncture time, time of each pass finish, time of initial flow restoration, time of successful recanalization and the end of the procedure
- eTICI score: pre-procedure and post-procedure
- Details of procedure: Accessory and adjunctive devices used (guide catheter, guidewire, intermediate catheter, microcatheter), number and type of devices for thrombectomy, number of recanalization attempt deployments, rescue procedures with medications besides thrombectomy
- Medication during the procedure: heparin, tirofiban, alteplase, urokinase.
- Intraprocedural complications: Presence of vasospasm (time of onset, vessels involved, time resolved, treatment required), evidence of clot migration or embolization, dissection, perforation, etc.

8.3 Post Treatment (Through Hospital Discharge)

A face-to-face observation will be performed at 36 hours (±12 hours) and 7 days (± 1 day)/at discharge whichever is earlier after randomization.

- Brain imaging performed at 36 (±12) hours after randomization: CT/CTA or MRI/MRA.
- A physical exam, as well as clinical and neurological assessments, will be completed at 36 (±12) hours and 7 (±1) days/at discharge whichever is earlier after randomization. Data to be collected include: vital signs (blood pressure and heart rate), relevant concomitant medications (including antiplatelet, anticoagulant, and antihypertensive agents), significant findings from clinical assessment and physical exam (i.e. all new, worsening, or improved conditions), all significant neurological findings, NIHSS Score (both), mRS (7 days or discharge only), and adverse event (AE).
- Head CT evaluation is needed at 7 days (±1 day) or at discharge whichever is earlier
- Laboratory examinations will be collected at 24 hours (±12 hours) and 7 days (± 1 day) or at discharge whichever is earlier after randomization, including: blood routine, renal function, liver function, coagulation, fasting blood glucose, etc.

8.4 Follow-up Visit at Day 30 (±3), Day 90 (±7) and 12 Months (±14 days)

These follow-up evaluations can be performed via telephone if it's not convenient for an in-person visit at the investigational site. All subjects entered into the study will undergo a standard neurological assessment by experienced physicians who are blinded to treatment assignment. Data to be collected include:

- mRS
- Patient-reported functional health status and quality of life using EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D-5L)[34]
- Relevant concomitant medications
- Significant findings from clinical assessment and physical exam (i.e. all new, worsening, or improved conditions since discharge)

8.5 Unscheduled Follow-up Visit

If an unscheduled follow-up visit occurs after randomization at the investigational site during the study, the incidence of any new or unresolved AEs will be assessed. If the visit is due to a change in neurological status, NIHSS and mRS will be completed by a certified rater.

8.6 Schedule of activities and assessments

Measurements	Baseline	36-hour (±12 hours) visit	7±1 day /at discharge visit	30-day (±3 days) visit	90-day (±7 days) visit	12-month ±14 days visit
Informed Consent	x					
Inclusion/Exclusion	x					
Randomization	x					
Demographic characteristics	x					
History of present illness	x					
Past medical history	x					
Relevant Concomitant Medications	x	x	x	x	x	x
mRS	x		x	x	x	x
NIHSS	x	x	x			
Head CT	x		x[3]			
CTA±CTP or MRI*+MRA±PWI	x[1]					
CT+CTA or MRI*+SWI+MRA		x[2]				
Carotid CTA/MRA/ultrasound		x[4]				
ASPECTS on CT	x					
Ischemic volume on CTP/DWI	x	x[5]	x[5]			
Laboratory examinations	x	x	x			
Electrocardiogram	x					
TOAST			x			
EQ-5D-5L scale				x	x	x
AE/SAE		x	x	x	x	x

[1] For all enrolled cases, CT+CTA+CTP examination will be the first choice before randomization

[2] All the enrolled cases should be reviewed with multi-modal imaging 24-48 hours after randomization, and the imaging evaluation method should be the same as before randomization

[3] All enrolled cases should be examined by head CT at 7 days (±1 day) after randomization or at discharge whichever is earlier

[4] Only applicable to patients in the standard medical treatment group who did not undergo cervical angiography prior to randomization

[5] Based on head CT or MRI, determined by the core imaging laboratory

*MRI sequence includes T1+T2+DWI+ADC+FLAIR sequence

ADC: apparent diffusion coefficient; AE: adverse event; ASPECTS: Alberta stroke program early computed tomography score; CT: computed tomography; CTA: computed tomography angiography; CTP: computed tomography perfusion; EQ-5D-5L: EuroQoL 5-Dimensions 5-Level questionnaire; FLAIR: fluid attenuated inversion recovery; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; PWI: perfusion weighted imaging; SAE: serious adverse event; SWI: susceptibility weighting imaging; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

9. Study risk pre-assessment and risk management

9.1 Monitoring of adverse events

All AEs will be managed and reported in compliance with all applicable regulations and will be included in the final Clinical Study Report (CSR).

9.2 Definitions of adverse events

9.2.1 Adverse event (AE)

Adverse Events, as long as they occur from the first visit planned in the Clinical Trial Protocol/signature of the informed consent (i.e., occurring during the washout period) to the last visit planned in the protocol, are adverse medical events or deterioration of qualifying event. AEs include symptoms (ie, nausea, chest pain), signs (ie, tachycardia, liver enlargement) and abnormal laboratory results (ie, laboratory or ECG abnormalities). AEs can be classified as serious adverse events (SAEs) and non-serious AEs.

9.2.2 Serious adverse event (SAE)

A Serious adverse event refers to an event that：

- Results in death, or
- Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event

9.3 Recording of adverse events

Non-serious AE: Only some of the non-serious AEs will be collected from time of randomization throughout the treatment/follow-up periods to the Study Closure Visit. Other non-serious AEs are up to the investigator to decide whether to collect.

SAE: All SAEs will be collected and recorded.

9.4 Causal relationship between adverse events and study:

Attribution of: (1) Definite; (2) Probably; (3) Possibly; (4) Unlikely; (5) Not related; (6) Not applicable.

9.5 Obligation of the investigator regarding safety reporting

9.5.1 Adverse events

All AEs will be recorded on the corresponding page(s) in the CRF. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to the Investigational Product, corrective treatment/therapy given, outcome and his/her opinion about whether it is possible that the AE is caused by the study intervention, related to the index stroke, other cause, or intercurrent condition.

9.5.2 Serious adverse event

For SAEs, the investigator must immediately take corresponding measures:

Immediately notify the representative of the Monitoring Team, send the signed and dated corresponding pages in the CRF to the representative of the Monitoring Team,

and attach a photocopy of all examinations conducted and the examination dates. For laboratory results, include the laboratory normal ranges. The contact information (name, address and fax number) of the representative is on the Clinical Trial Protocol. These measures should be completed no later than **24 hours** after SAE.

Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly noted on all copies of source documents provided to the Sponsor.

9.5.3 Follow-up and risk management

The Investigator should take all appropriate measures to ensure the safety of the patients.

Screening of subjects should strictly follow the inclusion and exclusion criteria of the study. If an AE occurs during the study period, relevant evaluations will be performed, including blood routine examination, coagulation, creatinine, hepatic function, renal function, arterial blood gas analysis, ultrasound and computer tomography. Targeted treatment and necessary consultation should be carried out in a timely manner. When addressing SAEs, it is important to make sure the patient’s airway is clear, respiration, blood pressure and heart rate are stable.

Notably, the investigator should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc.) until the patient's condition returns to normal or stabilizes. The follow-up will continue even if the patient withdraws from the clinical trial, and the patient will be interviewed by telephone or face-to-face at the scheduled visit time. The monitoring team may request additional visits and investigations.

10. Statistical Analysis

10.1 Sample size estimation

In this study, a multicenter, open, randomized, parallel control design method will be used. The primary measure of efficacy will be the mRS score at 90 days (±7 days) after enrollment

(considered as ordered variable). According to the literature data and clinical expert opinions, the parameters were set as follows: (1) The proportion of mRS score 0-6 in control group will be 3%, 4%, 10%, 17%, 16%, 12% and 38%, respectively; (2) The average treatment effect of EVT improves the outcome with the common OR value for improvement of mRS reaching 1.74; (3) Two Interim analysis are considered. The adjusted level α is 0.050 and power 1-β is 0.90. (4) The randomization will be allocated to the intervention and the control group in a 1:1 ratio. Based on these parameters, the sample size will be 219 in each group. Considering a 10% attrition rate, the final total sample size will be 488 patients, with 244 patients in each group.

Interim analysis will take place when 1/2 (244) and 3/4 (366) of patients will have completed 3-month follow-up." The corresponding significance levels based on the O'Brien & Fleming boundary are 0.003 (stage 1), 0.018 (stage 2) and 0.044 (stage 3, final analysis).

The PASS software (NCSS, LLC, version 11) was used to calculate the sample size.

10.2 Data collection and entry

Paper-based CRF and electronic data capture (EDC) system will be used for data collection and input. All the content required by the protocol in the system must be filled. The unfilled content should be explained, and the reason needs to be marked in the EDC system.

10.2.1 Paper-based CRF filled out by the investigator

Site investigators should use black or blue-black recording pens to fill out the paper-based CRF neatly and clearly to ensure that the data is clear and readable. If the paper-based CRF information needs to be modified, it should not be altered or overwritten. The correct information should be written next to the original information, signed and dated by the person who modified it. The clinical research monitor (Clinical Research Associate, CRA) will review the completeness and accuracy of the CRF and guide the investigator to make necessary corrections and supplements.

10.2.2 Data entry to the EDC system by CRC

After the paper-based CRF is completed, the Clinical research coordinator (CRC) will

input the content of the paper CRF into the EDC system.

10.2.3 Submission to the EDC system after the approval of the investigator

The paper-based CRF will be submitted after the investigator has approved it. After the data is submitted, all data revisions and feedback are carried out through the EDC system. If the EDC system has submitted a form that needs to be modified, contact the CRA of this center. After the CRA opens the form, the investigator can guide the CRC to modify the data in EDC system.

10.2.4 Data monitoring and query by CRA via EDC

10.2.5 Data exportation from the EDC system

After the data from the EDC system is exported to the database, it will be proofread by the data administrator. Obvious errors will be corrected by the data administrator. Other errors or missing values will be filled in the data query form, and the query form will be sent to the participating center for solutions through email, express, telephone or WeChat.

The participating centers are responsible for correcting the data in the EDC system after verifying the original data and related information. Site investigators must answer these queries by verifying or modifying relevant information or data.

10.3 Statistical considerations

This section is an overview of the statistical considerations. It provides the general specifications for the analysis of the data to be collected and presented in the CSR. A final Statistical Analysis Plan (SAP) will be issued prior to database lockdown and before code breaking. The SAP will define all “pre-specified, planned analyses.”

All programming will be performed using SAS Version 9.4.

10.3.1 Analysis sets

(1) Full Analysis Set (FAS):

Based on the principles of the Intent-to-Treat (ITT) analysis, all randomized subjects, either treated with medication or with EVT will be included in the FAS. The primary efficacy endpoint analysis of this study will be performed on the FAS.

(2) Per Protocol Set (PPS)

The PPS is a subset that includes all subjects who were treated with the treatment assignment to which they were randomized and there are no clinically meaningful deviations from the protocol. Severe deviations from the protocol will be defined during the data auditing process, including but not limited to the following:

1) The subject is not in line with the inclusion criteria.

2) There are other treatments that potentially confound the appraisal of efficacy of the planned treatment.

3) Poor compliance.

4) Follow-up interval exceeds the required time window.

Secondary analysis will be conducted on the PPS. If its result are not consistent with that of the FAS, a detailed analysis to examine the difference(s) will be required.

(3) Safety Analysis Set (SAS)

The SAS consists of all subjects who received treatment with at least one evaluation of the safety outcome.

10.3.2 Statistical considerations

(1) Baseline characteristics comparisons

T-test or Wilcoxon rank sum test will be used for comparison between continuous variables, and Chi-squared tests, Fisher's exact test or Wilcoxon sum rank test will be used for comparison between categorical variables.

(2) Efficacy Analysis

Primary efficacy endpoint: Based on an ITT basis, an ordinal logistic regression model is used to calculate the common odds ratio between the two treatment groups. All statistics will be two-sided with $p<0.05$ considered significant.

Secondary Efficacy Analyses: Endpoints including the 90-day mRS 0-2 will be analyzed using a binary logistic regression model. The infarct core volume change from baseline will be analyzed using student t-test or Wilcoxon rank sum test as appropriate.

(3) Safety Analysis

Safety events in the two treatment groups will be described based on the SAS dataset. Logistic regression will be used to compare the differences in safety endpoints such as intracranial bleeding events between the two groups. Chi-square test and Fisher's exact test will be used to compare the differences in the incidence of AEs and SAEs between the two groups.

(4) Subgroup analysis

The mRS at 90 days will be presented for each level of the covariates listed below:

(1) Age (< 70 years vs. ≥70 years)

(2) Last known well to randomization time (< 6 h vs. ≥ 6 h)

(3) Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16 points)

(4) IV thrombolysis or not

(5) Occlusion site (intracranial ICA vs. M1 segment)

(6) ASPECTS (< 3 points vs. ≥3 points)

(7) Infarct core volume (< 70ml vs. ≥70ml)

(8) Etiological subtype of stroke (cardiac embolism vs. large artery atherosclerosis)

10.4 Interim analysis

Interim analysis will take place when 1/2 (244 cases) and 3/4 (366 cases) have completed 3-month follow-up. The O'Brien-Fleming boundaries will be used at the interim analysis as follows:

There are no established techniques for the assessment of interim trial efficacy boundaries using an ordinal logistic regression model (proportional odds model). Instead, we will revert to a simple dichotomous analysis of the mRS score at 0-2 defined at 90 days from randomization. The Z-statistic for this analysis shall be derived from the normal approximation of the binomial distribution as an unadjusted two-sample test of proportions. For a RCT comparing two treatment groups with respect to a binary outcome and two interim analysis, corresponding significance levels based on the O'Brien & Fleming boundary are 0.003 (stage 1), 0.018 (stage 2) and 0.044 (stage 3, final analysis).

With the result of the interim analysis, the DSMB will make the decision to continue or halt the study according to the test boundaries. The study will stop prematurely for futility if the result from the interim analysis indicate that an effective conclusion with the current sample size can't be achieved. Premature stopping for early success will be achieved if the interim analysis result proves the effect of the intervention arm at significance level. Otherwise, the study will be continued until the predefined termination date. In interim analysis, the final sample size can be adjusted if the estimation of the primary outcome is drastically different from the actual data.

11. Ethical standards

11.1 Ethical standards

This Clinical Trial will be conducted in accordance with the principles set by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice. Prior to initiating the study, each site will obtain Institutional review board (IRB) or institutional ethics committee (IEC) approval for the protocol, informed consent forms and material used to recruit subjects. Before each subject is enrolled, the investigator is responsible for fully and comprehensively introducing the purpose, procedures and possible risks of the study to the patient or his/her agent, signing a written informed consent form, and informing the patient that he/she has the right to withdraw from this study at any time. The informed consent should be kept as a clinical

study document for future reference. The personal privacy and data confidentiality of subjects will be protected during the study process.

11.2 Law and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, Chinese laws and regulations, as well as any applicable guidelines.

11.3 Informed consent

The Investigator/sub-investigator should fully inform the patient of all pertinent aspects of the Clinical Trial, including the written information approved/preferred by the Ethics Committee (IRB/IEC). The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor and then submitted to the Ethics Committee (IRB/IEC) for approval.

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a patient's participation in the Clinical Trial, an informed Consent Form should be signed and dated by the patient or by the patient's legal representative and by the person who conducted the informed consent discussion. A copy of the signed and dated Informed Consent Form will be provided to the patient.

11.4 Institutional review board/ Institutional ethics committee (IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and the Ethics Committee is required to forward to the Sponsor a copy of the written approval/favorable opinion signed and dated by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.), the list of voting members along with their qualification and the date of the review should be clearly stated on the written (IRB/IEC) approval.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol

should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC). If requested, an annual progress report, as well as final summary of the Clinical Trial's outcome at the end of the Clinical Trial, will also be sent to the Ethics Committee (IRB/IEC).

12. Confidentiality and publication of research findings

The principal investigator has complete intellectual property rights. The entire research process and data analysis process will strictly protect the patient’s information. Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. The trial results will be published as soon as possible after database lockdown. This trial will produce detailed data on treatment effects, medical care, and outcomes. Biostatisticians will be consulted to ensure that it is impossible to uniquely identify any participant. Diskettes with the data in comma-delimited text format, along with a data dictionary in a text file, will be sent to interested parties.

13. Study Organization

13.1 Constitution

- **The steering committee**

  - ✓ The steering committee will provide scientific and strategic direction for the trial and will have overall responsibility for its design, execution, and publication.
  - ✓ The steering committee will also be responsible for ensuring that study execution and management are of the highest quality.

- ✓ It will approve the protocol and the operational guidelines of the trial prior to its commencement.
- ✓ The steering committee will meet regularly by teleconference or face-to-face meetings to discuss and report the progress of the study.
- ✓ The composition of the steering committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

- **Executive committee**

The executive committee is responsible for reviewing the status of the trial and available blinded data and will take appropriate actions regarding the conduct of the study. Executive Committee meetings will be organized to make major decisions. The composition of the Executive Committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

- **Data safety and monitoring board (DSMB)**

The DSMB will meet regularly and monitor the study progress to ensure that the study meets the highest standards of ethics and patient safety. It is composed of Academic Members, including an independent statistician, who does not participate in the trial. A DSMB charter including membership, role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial.

Written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting.

- **Clinical event committee (CEC)**

Clinical events and safety endpoint will be reviewed by CEC. A CEC charter including membership, role and responsibilities will be approved before the start of the trial by the CEC and the Executive Committee.

- **Imaging assessment committee**

13.2 Site training and certification

The executive committee will provide training to their participating sites in Good Clinical Practice Guidelines and in some outcome assessments. Prior to initiation of patient enrollment, Site Investigators and Coordinators must complete all training programs.

The training programs that need to be completed are as follows:

(1) Study procedures
(2) ANGEL-ASPECT eligibility criteria
(3) mRS
(4) NIHSS
(5) ASPECTS
(6) iSchemaView automated RAPID® software
(7) eTICI
(8) TOAST etiology subtyping
(9) Heidelberg Bleeding Classification
(10) Collecting DICOM imaging data

Successful completion of the training program is mandatory before a site begins to enroll patients. A conference call will be held intermittently, and PI and key staff will be available to answer questions.

A detailed Manual of Procedures will serve as the primary document describing all study related procedures. It will serve as a guide to train clinical center personnel and will be updated periodically throughout the study on the ANGEL-ASPECT website, as needed. A system composed of members of the executive committee and CRA will be implemented for the clinical centers to ask any procedural questions by phone, fax, or e-mail. The ANGEL-ASPECT executive committee and monitoring committee will formulate answers in consultation with the Steering Committee and will periodically distribute to the participating centers a set of frequently asked questions and answers.

The members of the executive committee will manage and conduct site visits to ensure the integrity and validity of the data on the CRF. During the trial period, each site should be visited at least once. If there are data quality problems or recruitment problems, it should be visited as needed.

14. Study monitoring and quality assurance control

14.1 Responsibilities of the investigator(s)

The Investigator(s) should conduct the Clinical Trial in accordance with the Clinical Trial Protocol, The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator should provide reliable data and all information requested by the Protocol (with the help of the CRF, Discrepancy Resolution Form or other appropriate instruments) in an accurate and legible manner and ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint other individuals as Sub-Investigators, as he/she thinks appropriate. All Sub-Investigators shall be appointed and listed in a timely manner and will be supervised by the Investigator. The Investigator will provide them a copy of the Clinical Trial Protocol and all necessary information. The Sponsor is responsible for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards to ethics, Clinical Trial Protocol compliance, integrity and validity of the data on the CRF.

14.2 Study monitoring

The main responsibility of the monitoring team is to help researchers to ensure that

all aspects of clinical trials are ethical, scientific, professional, and standardized. According to the ICH guidelines for Good Clinical Practice (GCP), the Monitoring Team must check the CRF entries according to the source documents, except for the pre-identified.

The monitoring team will regularly contact each center through site visits or an online webinar, and will send inspectors to evaluate the research progress, adherence of the investigators and patients to the research protocol and to solve urgent problems. During these inspection visits, the inspector will work together with the site-investigators. The main aspects of inspection and monitoring are as follows (not exclusive): patient's informed consent, patient recruitment and follow-up, documentation and reporting of SAEs and data quality.

15. Data retention

The double reviewed CRF and imaging data will be sent to the trial-designated data management center by CRAs. The person in charge of the data management center will check and sign the receipt form. The CRF will be kept by the research center after data entry is completed.

16. Data Security Monitoring

The data safety monitoring board (DSMB) is established to monitor the safety of participants, protect participants and ensure the integrity of the study. All AEs should be recorded, handled and tracked until they are properly resolved or stabilized. Any SAEs and unexpected events should be reported in a timely manner to the ethics committee in accordance with the relevant provisions, the competent department, the sponsor and the supervisory and administrative departments. The principal researchers should regularly review all AEs and set up meetings to assess the risks and benefits of the study if necessary. An independent data safety monitoring committee will be

appointed to review safety data, evaluate the effectiveness of data monitoring, and decide whether to make new proposal.

During the clinical trial, the data of the subjects should be collected anonymously in the CRF. The subjects are identified only by the subject number and the abbreviation of the initials. Due to safety reason and administrative instructions, when the subject's identity is leaked, researchers shall share the responsibility of confidentiality. In the informed consent form, the patient allows authorized research staff, ethics committee, and the authority to refer directly to the relevant original data on the case report (such as the patient's medical file case, booking records, the original laboratory records, etc.). The above personnel shall comply with occupational confidentiality rules and must keep all patient identity and medical information confidential.

17. Registration and Publication

17.1 Registration of study summary and results

The study representatives will register a study summary in ClinicalTrials.gov (https://clinicaltrials.gov) before the start of the study and update the summary as appropriate according to changes in the protocol or progress of the study. When the study is completed, the study representatives will register a study result without delay.

17.2 Publication of study results

When the study is completed, the study database will be closed within one month after the last scheduled follow-up date of the last included patient. A manuscript which describes the study and the answer to the primary research question will be submitted to a major clinical journal within 3 months from closure of the database. The study representatives will publish the results of the study after taking necessary measures (e.g., to prevent identification of specific study patients) to protect the human rights of patients and related parties or the rights and benefits of patients and related parties.

The manuscript will be shared with the financial sponsor(s) one month before submission, but the financial sponsor(s) will have no influence on its contents. Author(s) of the paper are determined by the study representatives according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http: //www.icmje.org/) by the International Committee of Medical Journal Editors (ICMJE). All authors should review and agree to the details of the paper prior to submission. The same goes for authors of conference presentations.

18. Ownership and use of data

18.1 Ownership of the data

The results, data, intellectual property rights, etc. obtained in this study belong to the study representatives and not to the patients. Whether the intellectual property rights of the study representatives belong to the individual or to the study institution is determined by the agreement of the participating hospital.

18.2 Use of collected data

The study Steering Committee determines whether to use the data obtained in this study (hereinafter, “study data”) for further study conducted by the Study representatives or sub-investigators as a secondary analysis.

If the analysis is judged to be beyond the scope of secondary analysis, or if the study data is used by a person except for the study representatives or sub-investigators of this study, the Study Steering Committee prepares a separate protocol and conducts the study after undergoing ethical review in accordance with relevant laws, regulations and ethical guidelines for medical research on human subjects.

19. Funding and conflict of interest

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20. Reference

1. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50(12):e344-e418. DOI: 10.1161/STR.0000000000000211.
2. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO)- European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. J Neurointerv Surg 2019;11(6):535-538. DOI: 10.1136/neurintsurg-2018-014568.
3. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20. DOI: 10.1056/NEJMoa1411587.
4. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18. DOI: 10.1056/NEJMoa1414792.
5. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30. DOI: 10.1056/NEJMoa1414905.
6. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306. DOI: 10.1056/NEJMoa1503780.
7. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95. DOI: 10.1056/NEJMoa1415061.
8. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med 2018;378(1):11-21. DOI: 10.1056/NEJMoa1706442.
9. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med 2018;378(8):708-718. DOI: 10.1056/NEJMoa1713973.
10. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15(11):1138-47. DOI: 10.1016/S1474-4422(16)30177-6.
11. Gautheron V, Xie Y, Tisserand M, et al. Outcome After Reperfusion Therapies in Patients With Large Baseline Diffusion-Weighted Imaging Stroke Lesions: A THRACE Trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) Subgroup Analysis. Stroke 2018;49(3):750-753. DOI: 10.1161/STROKEAHA.117.020244.
12. Deb-Chatterji M, Pinnschmidt H, Flottmann F, et al. Predictors of independent outcome of thrombectomy in stroke patients with large baseline infarcts in clinical practice: a multicenter analysis. J Neurointerv Surg 2020;12(11):1064-1068. DOI: 10.1136/neurintsurg-2019-015641.

13. Roman LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018;17(10):895-904. DOI: 10.1016/S1474-4422(18)30242-4.
14. Campbell BCV, Majoie C, Albers GW, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol 2019;18(1):46-55. DOI: 10.1016/S1474-4422(18)30314-4.
15. Sarraj A, Hassan AE, Savitz S, et al. Outcomes of Endovascular Thrombectomy vs Medical Management Alone in Patients With Large Ischemic Cores: A Secondary Analysis of the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) Study. JAMA Neurol 2019;76(10):1147-1156. DOI: 10.1001/jamaneurol.2019.2109.
16. Cagnazzo F, Derraz I, Dargazanli C, et al. Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS </=6: a meta-analysis. J Neurointerv Surg 2020;12(4):350-355. DOI: 10.1136/neurintsurg-2019-015237.
17. Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G. Triage imaging and outcome measures for large core stroke thrombectomy - a systematic review and meta-analysis. J Neurointerv Surg 2020;12(12):1172-1179. DOI: 10.1136/neurintsurg-2019-015509.
18. Rebello LC, Bouslama M, Haussen DC, et al. Endovascular Treatment for Patients With Acute Stroke Who Have a Large Ischemic Core and Large Mismatch Imaging Profile. JAMA Neurol 2017;74(1):34-40. DOI: 10.1001/jamaneurol.2016.3954.
19. Broocks G, Flottmann F, Schonfeld M, et al. Incomplete or failed thrombectomy in acute stroke patients with Alberta Stroke Program Early Computed Tomography Score 0-5 - how harmful is trying? European journal of neurology 2020;27(10):2031-2035. DOI: 10.1111/ene.14358.
20. Nicholson P, Hilditch CA, Neuhaus A, et al. Per-region interobserver agreement of Alberta Stroke Program Early CT Scores (ASPECTS). J Neurointerv Surg 2020;12(11):1069-1071. DOI: 10.1136/neurintsurg-2019-015473.
21. van Horn N, Kniep H, Broocks G, et al. ASPECTS Interobserver Agreement of 100 Investigators from the TENSION Study. Clin Neuroradiol 2021. DOI: 10.1007/s00062-020-00988-x.
22. Demeestere J, Garcia-Esperon C, Garcia-Bermejo P, et al. Evaluation of hyperacute infarct volume using ASPECTS and brain CT perfusion core volume. Neurology 2017;88(24):2248-2253. DOI: 10.1212/WNL.0000000000004028.
23. Sarraj A, Hassan AE, Grotta J, et al. Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT): A Prospective, Multicenter Cohort Study of Imaging Selection. Ann Neurol 2020;87(3):419-433. DOI: 10.1002/ana.25669.
24. Mourand I, Abergel E, Mantilla D, et al. Favorable revascularization therapy in patients with ASPECTS </= 5 on DWI in anterior circulation stroke. J Neurointerv Surg 2018;10(1):5-9. DOI: 10.1136/neurintsurg-2017-013358.
25. Inoue M, Olivot JM, Labreuche J, et al. Impact of diffusion-weighted imaging Alberta stroke program early computed tomography score on the success of endovascular reperfusion therapy. Stroke 2014;45(7):1992-8. DOI: 10.1161/STROKEAHA.114.005084.
26. Han M, Choi JW, Rim NJ, et al. Cerebral infarct volume measurements to improve patient selection for endovascular treatment. Medicine (Baltimore) 2016;95(35):e4702. DOI:

10.1097/MD.0000000000004702.

27. Manceau PF, Soize S, Gawlitza M, et al. Is there a benefit of mechanical thrombectomy in patients with large stroke (DWI-ASPECTS </= 5)? European journal of neurology 2018;25(1):105-110. DOI: 10.1111/ene.13460.
28. Broocks G, Rajput F, Hanning U, et al. Highest Lesion Growth Rates in Patients With Hyperacute Stroke. Stroke 2018:STROKEAHA118023457. DOI: 10.1161/STROKEAHA.118.023457.
29. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg 2014;6(2):83-6. DOI: 10.1136/neurintsurg-2013-010665.
30. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke; a journal of cerebral circulation 2015;46(10):2981-6. DOI: 10.1161/STROKEAHA.115.010049.
31. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke; a journal of cerebral circulation 2013;44(9):2650-63. DOI: 10.1161/STROKEAHA.113.001972.
32. Boers AM, Marquering HA, Jochem JJ, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. AJNR Am J Neuroradiol 2013;34(8):1522-7. DOI: 10.3174/ajnr.A3463.
33. Liu L, Chen W, Zhou H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke Vasc Neurol 2020;5(2):159-176. DOI: 10.1136/svn-2020-000378.
34. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208. DOI: 10.1016/0168-8510(90)90421-9.

21. Appendix

Appendix Table 1. Modified Rankin Scale

The modified Rankin Scale (mRS) is an ordinal scale ranging from 0 to 5, with higher scores indicating more severe disability. A score of 6 indicates death.

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Death	Death

Appendix Table 2. Extended Thrombolysis In Cerebral Ischemia (eTICI) Scale

eTICI grade	Short description	Long description
0	No perfusion	No antegrade flow beyond the point of occlusion
1	Limited reperfusion	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	<50% reperfusion	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
2b	≥50% and <90% reperfusion	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and its territories)
2c	≥90% reperfusion	Near complete antegrade reperfusion of the previously occluded target artery ischemic territory, except for slow flow or distal emboli in a few distal cortical vessels
3	100% reperfusion	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

MCA: middle cerebral artery; eTICI; extended thrombolysis in cerebral ischemia scale

Appendix Table 3. National Institute of Health Stroke Scale (NIHSS)

The NIHSS is an ordinal scale to evaluate the severity of stroke by assessing a patient's performance in the neurological exam. Scores range from 0 to 42, with higher scores indicating a more severe deficit. Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition
1a. Level of consciousness. The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Phasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiners not "help" the patient with verbal or non-verbal clues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hand cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.

two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be a 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, preexisting blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0= Normal. 1= Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2= Forced deviation; or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed in this case. If there is extinction, the patient receives a 1, and the results are used to respond to item 11.	0= No visual loss. 1= Partial hemianopia. 2= Complete hemianopia. 3= Bilateral hemianopia (blind including cortical blindness)
4. Facial palsy: Ask or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1= Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2= Partial paralysis (total or near-total paralysis of lower face) 3= Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and	0= No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1= Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2= Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against

clearly write the explanation for this choice.	gravity. 3= No effort against gravity; limb falls. 4= No movement. UN = Amputation or joint fusion: explain: 5a = Left Arm. 5b = Right arm.
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0= No drift; leg holds 30-degree position for full 5 seconds. 1= Drift; leg falls by the end of the 5-second period but does not hit bed. 2= Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3= No effort against gravity; leg falls to bed immediately. 4= No movement. UN = Amputation or joint fusion: explain: 6a. Left Leg 6b. Right Leg.
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0= Absent. 1= Present in one limb. 2= Present in two limbs. UN = Amputation or joint fusion: explain:
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0= Normal; no sensory loss. 1= Mild-to-moderate sensory loss; patients feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2= Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg.

9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0= No aphasia; normal 1= Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conservation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2= Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia: no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0= Normal. 1= Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood by some difficulty. 2= Severe dysarthria: patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier.
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0= No abnormality. 1= Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2= Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Appendix Table 4. EuroQoL 5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility

I have no problems in walking about	□
I have slight problems in walking about	□
I have moderate problems in walking about	□
I have severe problems in walking about	□
I am unable to walk about	□

Self-care

I have no problems washing or dressing myself	□
I have slight problems washing or dressing myself	□
I have moderate problems washing or dressing myself	□
I have severe problems washing or dressing myself	□
I am unable to wash or dress myself	□

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities	□
I have slight problems doing my usual activities	□
I have moderate problems doing my usual activities	□
I have severe problems doing my usual activities	□
I am unable to do my usual activities	□

Pain/discomfort

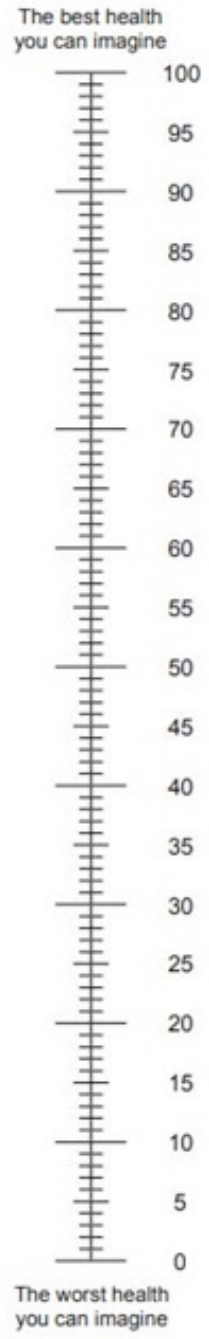
I have no pain or discomfort	□
I have slight pain or discomfort	□
I have moderate pain or discomfort	□
I have severe pain or discomfort	□
I have extreme pain or discomfort	□

Anxiety/depression

I am not anxious or depressed	□
I am slightly anxious or depressed	□
I am moderately anxious or depressed	□
I am severely anxious or depressed	□
I am extremely anxious or depressed	□

- We would like to know how good or bad your health is TOADY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALEH TOADY = [ ]



Appendix Table 5. Heidelberg bleeding classification

Symptomatic intracranial hemorrhage (SICH): new intracranial hemorrhage detected by brain imaging associated with any of the items below:

1. ≥4 points decline in the total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 point change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status

2. ≥2 point decline in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of ≥4 points on the NIHSS score

Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention.

3. Absence of alternative explanation for deterioration

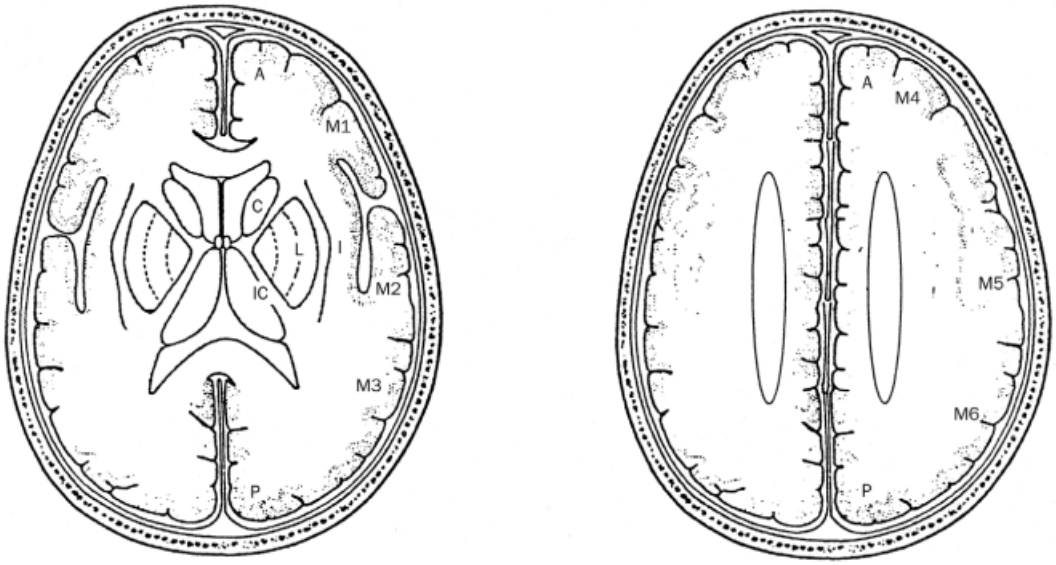
Anatomic Description of Intracranial Hemorrhages

Class	Type	Description
1	Hemorrhagic transformation of infarcted brain tissue	
1a	HI1	Scattered small petechiae, no mass effect
1b	HI2	Confluent petechiae, no mass effect
1c	PH1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2	Intracerebral hemorrhage within and beyond infarcted brain tissue	
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3	Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage	
3a		Parenchymal hematoma remote from infarcted brain tissue
3b		Intraventricular hemorrhage
3c		Subarachnoid hemorrhage
3d		Subdural hemorrhage

HI indicates hemorrhagic infarction; and PH, parenchymatous hematoma.

Appendix Table 6. Alberta Stroke Program Early CT Score (ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS) is a semiquantitative method of estimation of infarct size with non-contrast CT during the acute phase. The territory of the middle cerebral artery is allotted 10 points. 1 point is subtracted for an area of early ischaemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A normal CT scan has an ASPECTS value of 10 points. A score of 0 indicates diffuse ischaemia throughout the territory of the middle cerebral artery.



A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

Study of Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a LargE InfarCT Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial (ANGEL-ASPECT)

Protocol

Research team: Beijing Tiantan Hospital, Capital Medical University, Beijing, China

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Protocol Version 7.1

Trial Registration: ClinicalTrials.gov NCT04551664

Date: May 18, 2021

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Protocol Signature Page

I have read this protocol and agree to adhere to the requirements.

By signing this document we confirm that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

_____

Clinical Site

_____ _____

Site Principal Investigator Signature Date

ANGEL-ASPECT Protocol Synopsis

Official Title		Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial
Acronym		ANGEL-ASPECT
Sponsor		Beijing Tiantan Hospital, Capital Medical University
Study Centers		~50 centers in China
Statement of Hypothesis		Best medical management (BMM) combined with endovascular Therapy (EVT) might be superior to BMM alone in acute anterior circulation large vessel occlusive (LVO) patients with a large infarct core.
Study Objectives	**Primary objective**	To estimate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have improved neurological functional outcomes when treated with BMM plus EVT compared to BMM alone.
	Secondary objective	To estimate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have increased the risk of symptomatic intracranial hemorrhage (sICH) when treated with BMM plus EVT compared to BMM alone.
Study settings		Multicenter, Prospective, Randomized, Open-label, Blinded End-point (PROBE) design
Randomization		Participants will be randomized in a 1:1 ratio based on simple randomization of the central network

		randomization system to receive BMM plus EVT or BMM alone.
Sample Size		A total of 502 patients are planned to be enrolled. Interim analysis will take place when 1/3 (168 cases) and 2/3 (336 cases) have completed 3-month follow-up.
Effective Endpoints	**Primary Endpoint**	90 days (±7 days) modified Ranking Scale (mRS)
	Secondary Endpoints	(1) 90 days (±7 days) mRS 0-2 (2) 90 days (±7 days) mRS 0-3 (3) 36 hours (±12 hours) NIHSS 0-1 or decrease ≥10 from baseline (4) Infarct core volume change from baseline, at 7 days (±1 day) or at discharge assessed with NCCT or at 36 hours (±12 hours) assessed with MRI (5) 36 hours (±12 hours) target artery recanalization rate assessed with CTA or MRA
Safety Endpoints	**Primary Safety Endpoint**	Rate of sICH within 48 hours from randomization (Heidelberg Bleeding Classification)
	Secondary Safety Endpoints	(1) All-cause mortality within 90 days (±7 days) (2) Any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification) (3) Decompressive hemicraniectomy during hospitalization
Participants	**Inclusion Criteria**	**Center Inclusion Criteria**

		(1) Equipped with emergency department and neurology department for stroke patients (2) Equipped with stroke team operating on 24/7 (3) Capable of EVT and intravenous (IV) thrombolysis for acute ischemic stroke patients **Clinical Inclusion Criteria:** (1) Age 18-80 years (2) Presenting with symptoms consistent with acute ischemic stroke (3) Pre-stroke mRS score 0-1 (4) NIHSS score 6-30 at the time of randomization (5) Randomization can be finished within 24 hours from stroke onset (stroke onset time is defined as last known well time) (6) Informed consent signed **Neuroimaging Inclusion Criteria:** (1) CTA or MRA proved occlusion of Internal Carotid Artery (ICA) terminus or M1 segment of Middle Cerebral Artery (2) Imaging evidence of low Alberta Stroke Program Early CT Score (ASPECTS) (based on non-contrast CT) or large infarct Core (defined as rCBF <30% on CT perfusion or ADC<620 on MRI) fill one of the following criteria: 1) ASPECTS 3–5 2) ASPECTS >5 (6 h-24 h) with infarct core volume 70-100 ml 3) ASPECTS <3 with infarct core volume 70-100 ml

	Exclusion Criteria	**Center Exclusion Criteria** (1) Centers in which the number of acute ischemic stroke cases treated with endovascular procedures are less than 20 per year; (2) Incapable of complying with the protocol to proceed with the research. **Clinical Exclusion Criteria** (1) Females who are pregnant, or those of childbearing, potential with positive urine or serum beta Human Chorionic Gonadotropin test (2) Known severe allergy (more severe than skin rash) to contrast agents uncontrolled by medications (3) Refractory hypertension that is difficult to be controlled by drugs (defined as persistent systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg) (4) Known hemorrhagic tendency (including but not limited to): Baseline platelet count $< 100\times10^9$/L; Heparin was administered within 48 hours with aPTT≥35s; on anticoagulant therapy with warfarin and International Normalized Ratio (INR) > 1.7 (Patients with no history or suspected coagulopathy do not need to wait for laboratory results of INR or aPTT prior to enrollment) (5) Parenchymal organ surgery and biopsy were performed in the past one month (6) Any active bleeding or recent bleeding (gastrointestinal bleeding, urinary bleeding, etc.) in the past one month

		(7) Undergoing hemodialysis or peritoneal dialysis; Known severe renal insufficiency with glomerular filtration rate <30 ml/min or serum creatinine >220 mmol/L (2.5mg/dl) (8) Brain tumor (with mass effect) (9) The expected survival time is less than 1 year (such as comorbidity with malignant tumor, serious heart and lung diseases, etc.) (10) Participation in other interventional randomized clinical trials that may confound the outcome assessment of the trial (11) Other circumstances that the investigator considers inappropriate for participation in the trial or that may pose significant risks to patients (such as inability to understand and/or follow the study procedures and/or follow up due to mental disorders, cognitive or emotional disorders) **Neuroimaging Exclusion Criteria** (1) Midline shift or herniation, mass effect with effacement of the ventricles (2) Evidence of acute intracranial hemorrhage (3) Acute bilateral strokes or multiple intracranial vessels occlusions
Treatment Allocation	**Study Arm**	BMM plus EVT
	Control Arm	BMM alone
Follow-up schedule		Study visits will take place on day of randomization, at 36 hours (± 12 hours), 7 days (±1 day)/at discharge

	which is earlier, 30 days (±3 days), 90 days (±7 days) and 12 months (± 14 days).
Subgroup analysis	Subgroup analysis will be performed based on the following variables: (1) Age (< 70 years vs. ≥70 years) (2) Weak-up stroke or not (3) Last known well to randomization time (< 6 h vs. ≥ 6 h) (4) Stroke severity before randomization (NIHSS<16 points vs. NIHSS≥16 points) (5) IV thrombolysis or not (6) Occlusion site (intracranial ICA vs. M1 segment) (7) Ipsilateral carotid artery occlusion or not (8) ASPECT score (< 3 points vs. ≥3 points) (9) Infarct core volume (< 70ml vs. ≥70ml) (10) Etiological subtype of stroke (cardiac embolism vs. large artery atherosclerosis)
Study duration	August 2020 to October 2023 (enrolment completed at October 2022)

Abbreviations

ADC	Apparent Diffusion Coefficient
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
ASPECTS	Alberta Stroke Program Early CT Score
BMM	Best Medical Management
CEC	Clinical Events Adjudication Committee
CI	Confidence Interval
CRA	Clinical Research Associate
CRC	Clinical research coordinator
CRF	Case Report Form
CSA	Chinese Stroke Association
CT	Computer Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion Imaging
DAWN	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
DICOM	Digital Imaging and Communications in Medicine
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
DWI	Diffusion Weighted Imaging
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	EuroQoL 5-Dimensions 5-Level questionnaire
eTICI	Expanded Thrombolysis in Cerebral Infarction
EVT	Endovascular Therapy
FAS	Full Analysis Set
FLAIR	FLuid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GRE	Gradient Recalled Echo
GSR-ET	German Stroke Registry – Endovascular Treatment
ICA	Internal Carotid Artery
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
INR	International Normalized Ratio

IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
LICV	Large Infarct Core Volume
LLC	Limited Liability Company
LVO	Large Vessel Occlusive
MCA	Middle Cerebral Artery
MM	Medical Management
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCCT	Non-contrast computed tomography
NCSS	Number Cruncher Statistical System
NIHSS	National Institute of Health stroke scale
NMPA	National Medical Products Administration
OR	Odd Ratio
PASS	Power Analysis and Sample Size
PPS	Per Protocol Set
PROBE	Prospective, Randomized, Open-label, Blinded End-point
PWI	perfusion weighted imaging
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SELECT	Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke
sICH	Symptomatic intracranial hemorrhage
THRACE	Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke
TICI	Thrombolysis In Cerebral Infarction
T-NICE	Tiantan Neuroimaging Center of Excellence
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

1. Background

Large clinical trials on early and late window stroke patients have helped to establish the indications for endovascular treatment (EVT) of acute ischemic stroke (AIS) patients with large vessel occlusion (LVO). [1,2] This includes Alberta Stroke Program Early CT Scores (ASPECTS) score ≥ 6 patients within 6 hours,[3-7] and patients meeting DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial imaging criteria patient at 6-16 or 24 hours.[8,9] Since then, many clinical trials have undergone an expanding the indications of EVT for AIS patients with LVO. Whether patients with large infarct core volume (LICV) are suitable for EVT is one of the unanswered questions.

1.1 The rational of EVT for large infarct core volume

Several retrospective studies, prospective studies, and meta-analyses suggest that patients with LICV may benefit from EVT. The Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE) trial was one of these early randomized trials to enroll patients with ASPECTS<6.[10] A subgroup analysis of THRACE trial showed among 53 subjects with a diffusion-weighted imaging (DWI) volume of >70 ml, 12 (22.6%) patients of the EVT group had good clinical outcomes (mRS ≤ 2 at 90 days). [11] The prospective German Stroke Registry – Endovascular Treatment (GSR-ET) also showed that 22% of 152 thrombectomy patients with ASPECTS <6 achieved independence with mRS 0-2 at 90 days.[12] The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration pooled the data from the six trials. It showed a benefit of EVT over control was observed in patients with ASPECTS 0–4 or DWI-determined infarct core volume ≥ 70 ml. Functional improvement (mRS 0-2 at 90 days) rates in the EVT group compared with the control group were 25% vs. 14% and 30% vs.20%,

respectively.[13,14]

In the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) trial, the prespecified secondary analysis of 105 patients (of whom 62 received EVT) with ASPECTS ≤ 5 or CTP-determined ischemic core volume ≥ 50 ml showed that functional independence was achieved in 31% in the EVT group vs. 14% in the control group.[15] Incidence rates of death, neurologic decline, and symptomatic intracerebral hemorrhage (sICH) were similar in both groups. In addition, EVT was also associated with less infarct growth (44 vs. 98 mL; p=0.006) and smaller final infarct volume (97 vs. 190 mL; p=0.001) than medical management (MM).

One meta-analysis including 17 studies and 1378 patients with ASPECTS 0–6 (1194 EVT, 184 MT) found that mRS 0–2 was achieved in 30.1% of cases after EVT and in 3.2% after MM (OR 4.76, p=0.01).[16] The marked lower rate in the MM group compared to previous RCTs (HERMES: 14%, SELECT: 14%) is likely due to the imbalance of baseline characteristics of the patients in these retrospective studies . for example, the patients in MM group were older (75 years vs 68.7 years), had higher NIHSS scores (19 vs. 18), lower rate of intravenous (IV) thrombolysis (47.8% vs. 56.8%) and longer symptoms onset to admission time (130 min vs. 115 min). Successful recanalization (Thrombolysis in Cerebral Infarction (TICI) grade 2b–3) gave higher odds of mRS 0–2 than unsuccessful reperfusion (OR 5.2, p=0.001). Another pooled random-effect meta-analysis, including 12 studies of large core patients (ASPECTS <6 or ischemic core volume ≥ 50 ml), demonstrated increased functional independence (mRS 0–2) rates with EVT (25% vs 7%; pooled OR: 4.39, 95% CI: 2.53 to 7.64), and decreased mortality (23% vs. 33%; pooled OR: 0.53, 95% CI: 0.40 to 0.71).[17]

In a matched case-control study of 56 patients (28 pairs) with ICA, M1 and M2 occlusion and CTP-determined infarct core > 50mL, EVT led to higher rates of functional independence (90-day mRS 0-2, 25% vs 0%; p=0.04), and smaller final infarct volumes (87 vs 242 mL; p <0.001).[18] One control (4%) and two treatment patients (7%) developed a parenchymal hematoma type 2 (p>0.99). The rates of hemicraniectomy (7% vs 21%; p=0.10) and 90-day mortality (29% vs 48%; p=0.75)

were lower in the EVT arm. Sensitivity analysis for patients with a baseline infarct core volume greater than 70 mL (12 pairs) revealed a significant reduction in final infarct volumes (110 vs. 319 mL; p<0.001) but only a nonsignificant improvement in the overall distribution of mRS scores favoring the treatment group (p=0.18).

Interestingly, one observational cohort study included a consecutive sample of 170 patients with anterior circulation stroke and initial ASPECTS ≤ 5 (99 patients in the EVT group, 71 patients in the MM group). The study showed that clinical outcome after failed or incomplete EVT (TICI 0–2b) was significantly better compared to patients with MM only (median mRS 5, interquartile range 4–6 vs. 5–6, p=0.03). Failed EVT (TICI 0–2a) was not associated with a worse outcome than MM.[19]

1.2 Image modality to identify large infarct core volume

Generally speaking, there were two imaging evaluation methods for large infarct core, one is a semi-quantitative evaluation based on CT/MRI-ASPECTS, and the other was a quantitative evaluation based on CTP/MRI with the aid of automated artificial intelligence software. ASPECTS is a widely accepted tool used to assess infarct volume. In general, ASPECTS < 6 is regarded as a "large core infarct." However, multiple studies have shown low interrater agreement with ASPECTS.[20,21] An inaccurate ASPECTS can mis-assign patients between the EVT and control groups, weakening any trial conclusions. Quantitative determination of infarct core volume using CTP/MRI could compensate for poor consistency of ASPECTS.

Notably, the correlation between the CTP/MRI-determined infarct core volume and ASPECTS is not well established. Therefore, the optimal imaging modality for evaluating patients with LICV in clinical trials remains to be explored. The subgroup analysis in a meta-analysis comparing outcomes between these two imaging modalities did not find significant heterogeneity in the results when LICV was defined based on ASPECTS or ischemic core volume of CTP.[17] While one study[22] found a good correlation between ASPECTS and CTP/MRI volume, others found them to be discordant.[15,17,23] To expedite enrollment, this study allowed the use of non-contrast CT

(NCCT)-ASPECTS and/or CTP/MRI imaging modalities to screen patients with LICV.

1.3 ASPECTS and infarct core volume selection

A recent meta-analysis of 17 studies and 1378 patients reported mRS 0-2 was achieved by 37.7%, 33.3%, 22.1%, and 17.1% of patients with ASPECTS 6, 5, 4 and 0-4 respectively.[16] The studies by Mourand et al.[24] and Inoue et al.[25] showed favorable outcomes in between 16% and 20% of patients with ASPECTS 0–3 after EVT. Another meta-analysis showed that ASPECT 0-2 favored MM instead of EVT.[13] The benefit of EVT gradually declined with decreasing in ASPECTS, especially when ASPECTS < 3, because the infarct core volume was very large and there was less salvageable brain tissue, which might make EVT ineffective.[13,26,27] Therefore, this study limited the ASPECTS of enrolled patients to 3-5.

There is some debate about whether "large core" should be defined as 50ml vs. 70ml on CTP. In ANGEL-ASPECT, the infarct core volume > 70 ml was defined as LICV. Similar to patients with ASPECTS 0-2, patients with excessive infarct core volume may also be less likely to benefit from EVT. Previous studies showed a lack of benefit if CTP-determined core volume exceeded 100 ml and 150 ml.[14,15] Therefore, when patients were enrolled only based on the infarct core volume as assessed by CTP/MRI, this study limited the infarct core volume to 70 ml-100 ml.

1.4 EVT time window for large infarct core volume

Patients in the hyperacute phase of stroke showed increased ASPECTS lesion growth from imaging to recanalization, suggesting a benefit of faster recanalization in these patients.[28] A meta-analysis by Cagnazzo et al. demonstrated that a shorter time from onset to reperfusion was associated with a higher probability of functional independence after EVT in patients with ASPECTS 0–6.[16] The SELECT trial found that patients with LICV had a gradual decline in functional outcomes with prolonged treatment time, with a lower likelihood of benefit from EVT after 12 hours.[15] This

suggested that for LICV patients, the earlier EVT may be more beneficial. However, a recent meta-analysis found that patients with LICV did not show a significant difference in outcomes among studies reporting <6 hours, <12 hours, and <24 hours for stroke to EVT time windows.[17] This may be because most LICV patients presented in the early time window, reducing the power to detect the difference between early and late windows. The reason may also be that the efficacy of MM declines over time, thus preserving the efficacy of EVT. In this context, it is important to study whether EVT also benefits patients with LICV in the late time window, therefore the time window of ANGEL-ASPECT is 0-24 hours.

1.5 ANGEL-ASPECT Trial design

ANGEL-ASPECT trial is a PROBE study initiated by researchers to explore the effectiveness and safety of EVT in patients with anterior circulation large vessel occlusion with ASPECTS 3-5 or infarction core volume 70-100ml within 24 hours. ANGEL-ASPECT trial allows multiple imaging modalities to screen for LICV patients, but at the same time imposes certain limitations on the range of ASEPCTS or infarct core volume. The main purpose was to reduce the risk of EVT while enrolling as many LICV patients as possible. The primary image inclusion criteria of ANGEL-ASPECT was NCCT-ASPECTS 3-5, and the infarct core volume 70 ml-100 ml was used as auxiliary inclusion criteria. Briefly, the inclusion criteria for LICV are: (1) If NCCT-ASPECTS is 3-5 and presentation is within 24 hours of onset, patients are enrolled without limitation of infarct core volume. (2) For NCCT-ASPECTS 0-2 and core infarction volume 70 ml-100 ml, patients are enrolled. (3) If NCCT-ASPECTS is >5 and between 6 to 24 hours from symptom onset, only patients with infarct core volume 70 ml-100 ml are enrolled.

Subgroup analysis will focus on age, LKW to randomization time, NIHSS score, IV thrombolysis, occlusion site, ASPECTS, infarct core volume, and stroke etiology.

ANGEL-ASPECT is the only randomized controlled trial conducted in China for LICV patients so far. The results of this trial will clarify whether EVT is effective and

safe in Chinese LICV patients.

2. Study objective

2.1 Primary objective

To estimate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have improved neurological functional outcomes when treated with BMM plus EVT compared to BMM alone.

2.2 Secondary objective

To estimate if acute ischemic stroke patients with anterior circulation LVO and large infarct core at 0-24 hours after stroke onset have increased the risk of sICH when treated with BMM plus EVT compared to BMM alone.

3. Study design

3.1 Study design

Multicenter, Prospective, Randomized, Open-label, Blinded End-point (PROBE) trial design (Figure 1).

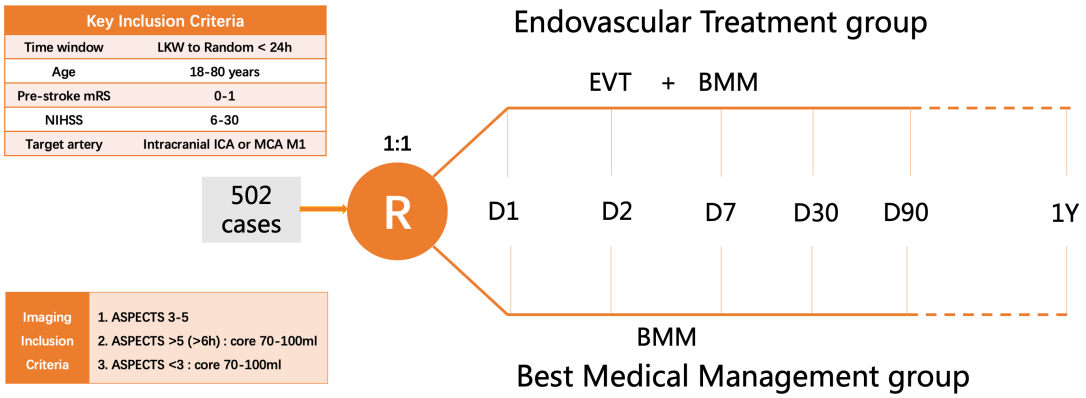

Figure 1. Study design: randomization algorithm

3.2 Randomization

The random code will be generated by a central network randomization system with 24h real-time online service based on the simple randomization method. The researcher in each center will obtain the random code from the central network randomization system according to the enrollment order. Patients who meet the inclusion criteria and in whom written informed consent can be obtained, will be randomly assigned to the following treatment groups in a 1:1 ratio:

- BMM plus EVT group: patients will receive EVT with stent retriever or contact aspiration as first-line devices for thrombectomy plus BMM;
- BMM group: Patients will receive BMM alone.

3.3 Follow-up schedule

(1) Face-to-face visit: day of randomization, 36 hours (±12 hours), 7 days (±1 day) /at discharge whichever is earlier

(2) Telephone visit: 30 days (±3 days), 90 days (±7 days), and 12 months ±14 days

3.4 Blind design

(1) Only the patient and the treating physician are aware of the randomization

information, and the evaluation of information at baseline and in-hospital visits that relate to the study endpoints should be evaluated by an investigator who is not aware of the patient group assignment and the treatment received.

(2) The primary endpoint visits are standardized visits conducted by trained third party personnel who are not aware of the patient's randomization assignment and their actual treatment status. All follow-up calls were recorded, and a follow-up report was formed.

(3) All imaging data related to the study will be collected for central interpretation. The images at each visit site were interpreted independently by a core lab, and the readers were unaware of the patient's baseline information, treatment received (except EVT angiography images), and prognosis.

4. Participant selection

4.1 Inclusion Criteria

4.1.1 Center Inclusion Criteria

(1) Equipped with an emergency department and neurology department for stroke patients

(2) Equipped with a stroke team operating 24/7

(3) Capable of endovascular therapy and IV thrombolysis for acute ischemic stroke patients

4.1.2 Clinical Inclusion Criteria

(1) 18 to 80 years of age

(2) Presenting with symptoms consistent with an acute ischemic stroke

(3) Pre-stroke mRS score 0-1

(4) NIHSS score 6-30 at the time of randomization

(5) Randomization can be finished within 24 hours of stroke onset (stroke onset time is defined as last known well time)

(6) Informed consent signed by the patient or legally authorized representative

4.1.3 Neuroimaging Inclusion Criteria

(1) CTA or MRA proven occlusion of the Internal Carotid Artery (ICA) terminus or M1 segment of the Middle Cerebral Artery (MCA)

(2) Imaging evidence of low ASPECTS (based on NCCT) or large infarct Core (defined as rCBF <30% on CT perfusion or ADC<620 on MRI) fulfill one of the following criteria:

4) ASPECTS 3-5

5) ASPECTS >5 (6h-24 h) with infarct core volume 70-100 ml

6) ASPECTS <3 with infarct core volume 70-100 ml

4.2 Exclusion Criteria

4.2.1 Center Exclusion Criteria

(1) Centers in which the number of acute ischemic stroke cases treated with endovascular procedures are less than 20

(2) Centers that are unable to comply with the research protocol

4.2.2 Clinical Exclusion Criteria

(1) Females who are pregnant, or those of childbearing potential with positive urine or serum beta Human Chorionic Gonadotropin test

(2) Known severe allergy (more than a rash) to contrast media uncontrolled by medication

(3) Refractory hypertension that is difficult to control by medication (defined as persistent systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)

(4) Known hemorrhagic tendency (including but not limited to): Baseline platelet count < 100×10^9/L; Heparin was administered within 48 hours with aPTT≥35s; on anticoagulant therapy with warfarin and International Normalized Ratio (INR) > 1.7 (Patients with no history or suspected coagulopathy do not need to wait for laboratory results of INR or aPTT prior to enrollment)

(5) Parenchymal organ surgery and biopsy were performed in the past one month

(6) Any active bleeding or recent bleeding (gastrointestinal bleeding, urinary bleeding, etc.)

in the past one month

(7) Undergoing hemodialysis or peritoneal dialysis; Known severe renal insufficiency with glomerular filtration rate <30ml/min or serum creatinine >220mmol/L (2.5mg/dl)

(8) Brain tumor (with mass effect)

(9) The expected survival time is less than 1 year (such as comorbidity with malignant tumor, advanced heart or lung disease, etc.)

(10) Participation in another interventional randomized clinical trials that may confound outcome assessment of the study

(11) Other circumstances that the investigator considers inappropriate for participation in the study or that may pose significant risks to patients (such as inability to understand and/or follow the study procedures and/or follow up due to mental disorders, cognitive or emotional disorders)

4.2.3 Neuroimaging Exclusion Criteria

(1) Midline shift or herniation, mass effect with effacement of the ventricles

(2) Evidence of acute intracranial hemorrhage

(3) Acute bilateral strokes or multiple intracranial vessel occlusion

5. Imaging protocol

5.1 Baseline imaging

All researchers were trained in the course of the imaging protocol and the use of RAPID software, and participated in the network training, simulation test and examination of NCCT-ASPECTS before enrollment. The ASPECTS training and test are conducted through the online training system of the trial website (http://angel-aspect.org). Those who pass the exam (accuracy rate more than 80%) will obtain the ASPECTS assessment qualification certificate and be qualified for imaging assessment. During imaging screening, researchers in the sub-center with imaging evaluation qualifications and two trained neuroradiologists from the trial team will conduct real-

time online image evaluation of ASPECTS, occlusion site, infarct core volume to ensure the accuracy of the imaging assessment (Figure 2).

(1) **ASPECTS:** All patients presenting within 24h of symptom onset will undergo a plain CT scan. After the preliminary screening of ASPECTS by trained clinicians in research centers, two dedicated clinicians (insert initials here / names) from the trial team will conduct real-time online evaluation of the prospective patient. When the ASPECTS score reaches a consensus that is between 3 to 5 between the site and central core lab investigators, the patient is then deemed suitable for enrollment into ANGEL-ASPECT. NCCT-ASPECTS will be manually determined independently before RAPID ASPECTS® (version 5.0.4, iSchemaView, CA, USA) assessment.

(2) **Infarct core volume:** The infarct core volume was automatically evaluated by iSchemaView automated RAPID® software (version 5.0.4, iSchemaView, CA, USA), and the infarction core volume was defined as rCBF<30% based on CTP or ADC<620 $\times 10^{-6}$ mm^2/s based on MRI. For patients who present with NCCT-ASPECTS 0-2 within 6 hours from symptom onset, if the infarct core volume is between 70ml and 100ml, then the patient is eligible for enrollment. If the infarct core volume is between 70ml and 100ml in an extend time window (6-24 hours) of stroke onset, the patient is also suitable for inclusion regardless of ASPECTS.

(3) **Target occlusion vascular:** The occluded arterial was determined by CTA or MRA. Occlusion of the ICA or M1 segment of the MCA is suitable for enrollment. Patients with ipsilateral extracranial internal carotid artery occlusion or stenosis with the above artery occlusion will also be included in this trial. As a tandem lesion can be difficult to distinguish on CTA or MRA, patients with tandem lesion in the EVT group will be confirmed during angiography.

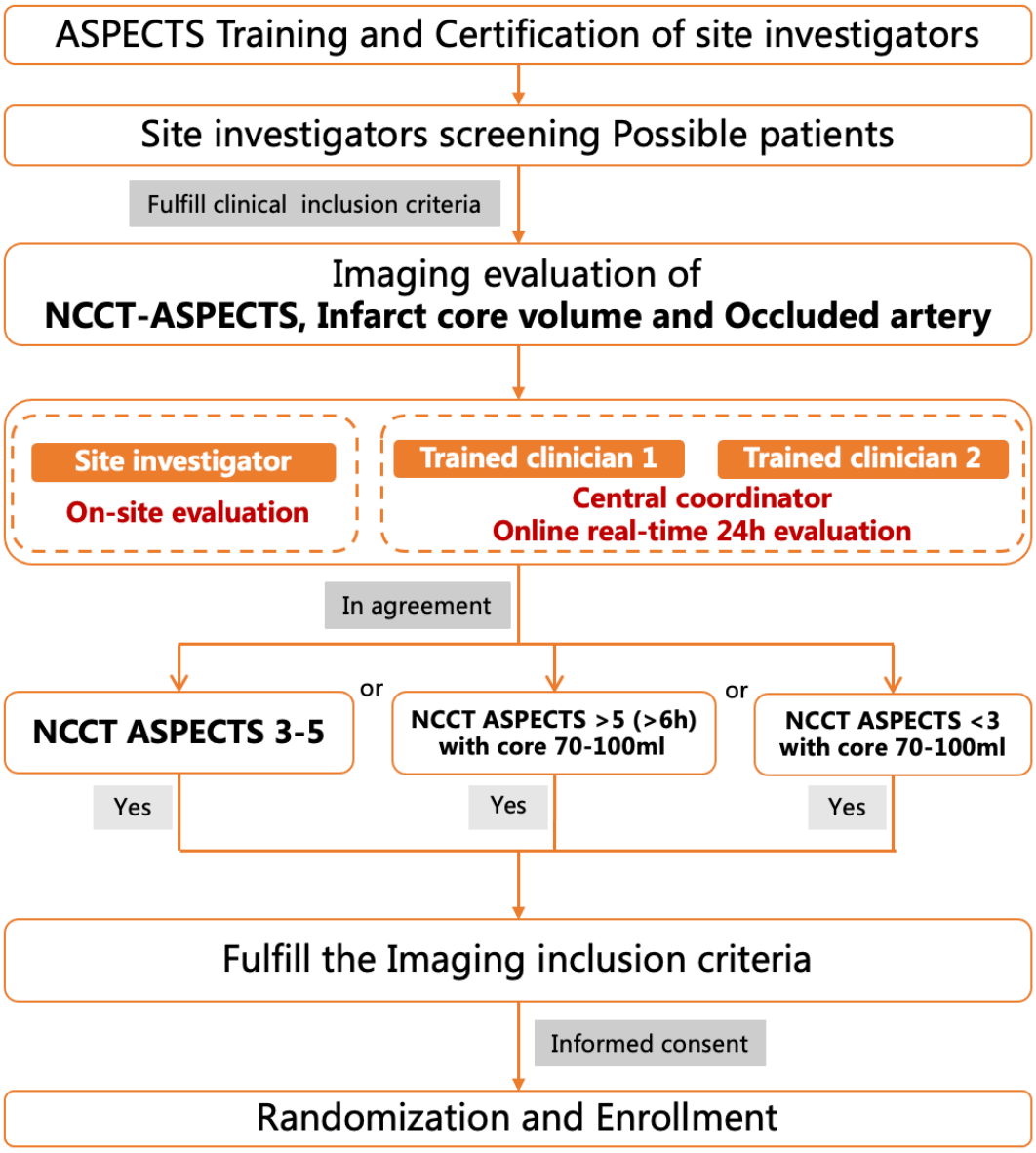

Figure 2. Imaging evaluation working flow

5.2 Intraoperative and follow-up imaging:

(1) **Intraoperative imaging:** In the EVT group, preoperative DSA was required to determine the site of vascular occlusion and eTICI score,[29] and postoperative angiography was required to evaluate the eTICI score. It is recommended to conduct NCCT or cone-beam CT immediately after EVT to exclude bleeding.

(2) **Imaging evaluation of hemorrhage:** The NCCT scan 36 hours (±12 hours) after randomization was taken as the main criterion for the judgment of hemorrhage, and

Heidelberg Bleeding Classification was used to evaluate the classification of hemorrhage.[30]

(3) **Vascular imaging follow-up:** Vascular imaging (CTA/MRA) was conducted with 36 hours (±12 hours) h after randomization to determine vascular patentability.[31]

(4) **Evaluation of postoperative infarct volume:** The infarct core volume was determined at 7 days (±1 day) or at discharge assessed with NCCT or at 36 hours (±12 hours) assessed with MRI, and the infarct core volume was determined manually by imaging core lab using validated automated software.[32]

5.3 Imaging core lab

Tiantan Neuroimaging Center of Excellence (T-NICE) is the imaging core lab of this trial. During the period from onset to discharge, all imaging data (CT, CTA, CTP, MRI, MRA, PWI, DSA) were collected by CRO in DICOM format. T-NICE will conduct quality control. All images will be quality controlled, rendered anonymous and sent to T-NICE for central adjudication. The final results will be reviewed and confirmed by the imaging assessment committee, and then input into the database system.

6. Treatments

Patients meeting the eligibility criteria and signing the informed consent will be randomized. Patients randomized to the interventional arm will receive BMM plus EVT. Artery puncture should be performed within 1 hour of randomization. Patients randomized to the medical arm will receive BMM.

6.1 Endovascular Therapy (EVT)

When the patient's condition permits, local anesthesia is the first choice for rapid initiation of puncture and endovascular therapy. If the condition requires, sedation can be used, and intubation can be considered for patients at high risk of airway collapse.

If the patient is expected to have poor intraoperative cooperation even with sedation or is at high risk of using sedation or airway conditions due to the patient's illness, general anesthesia should be used. Return to the Neuro-Intensive Care Unit (NICU) with intubation or not should be determined according to the surgical results.

Systemic heparinization is not recommended for preoperative and intraoperative treatment. Femoral artery is suggested for arterial puncture, and long sheath, guiding catheter or balloon guiding catheter can be used. Stent retriever (Solitaire, EMBOTRAP, Reco, Captor or other first-line stent retriever systems) and/or contact aspiration (Penumbra aspiration system or other first-line aspiration system) are recommended as the first choice for thrombectomy. If successful reperfusion (eTICI 2b50-3) is not achieved after routine thrombectomy, other techniques are allowed for rescue treatment, including replacement of thrombectomy technique, replacement of thrombectomy device, intra-arterial thrombolysis, balloon angioplasty or stent implantation, etc. The need for rescue treatment is defined (including, but not limited to, a decision made by the investigator based on intraoperative conditions) as follows: three times of thrombectomy with the same thrombectomy device (stent or suction catheter) without successful recanalization; Target vessels were successfully recanalized and reoccluded again; Target vessel dissection or stenosis ≥70%, with any degree of forward blood flow disturbance; New lumen/stent thrombosis resulted in a decreased of eTICI score.

All the above operations should be performed using devices approved by the National Medical Products Administration (NMPA) and should be performed in accordance with the approved intended use and operating instructions.

6.2 Best Medical Management (BMM)

All enrolled patients should receive BMM in accordance with the recommendation of “Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders” by Chinese Stroke Association (CSA).[33] This includes IV thrombolysis therapy for patients meeting the guidelines. Patients who plan to undergo or are undergoing IV thrombolysis therapy can decide whether to terminate IV thrombolysis

therapy in advance according to the investigator's judgment after enrollment. Patients who had completed IV thrombolysis prior to randomization are also eligible for inclusion in this study. All patients will be required to record the name, dosage and time of IV thrombolysis medication in detail. Antiplatelet agents are not recommended within 24 hours after IV thrombolysis unless the patient has undergone balloon dilatation or stent implantation, at which time the antithrombotic strategy is determined by the investigator. Based on the time window and infarct core volume for ANGEL-ASPECT, it is anticipated that most patients enrolled in ANGEL-ASPECT will not have received IV thrombolysis prior to randomization. Non-IV thrombolysis patients will be treated with aspirin, unless an indication for early anticoagulation is present.

7. Study endpoints

7.1 Primary efficacy endpoint

90 days (±7 days) modified Ranking Scale (mRS)

7.2 Secondary efficacy endpoint

(1) 90 days (±7 days) mRS 0-2
(2) 90 days (±7 days) mRS 0-3
(3) 36 hours (±12 hours) NIHSS 0-1 or decrease ≥10 from baseline
(4) Infarct core volume change from baseline, at 7 days (±1 day) or at discharge assessed with NCCT or at 36 hours (±12 hours) assessed with MRI
(5) 36 hours (±12 hours) target artery recanalization rate assessed with CTA or MRA

7.3 Primary safety endpoint

Rate of sICH within 48 hours from randomization (Heidelberg Bleeding Classification, Appendix 5)

7.4 Secondary safety endpoint

(1) All-cause mortality within 90 days (±7 days)
(2) Any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification)
(3) Decompressive hemicraniectomy during hospitalization

8. Data collection and Study procedure

Investigator(s) should keep a record, the eligibility Case Report Form (CRF), of subjects who enter pre-study screening. The sub-center number must be indicated. The screening table will be used to analyze and determine whether the enrolled patients in different study sites are representative. Referring to the procedure manual and data collection guidelines, investigators should guarantee the input of CRF is precise, complete and timely, and answer the queries in time. Brain imaging which includes: CT, CTA, CTP, MRI (T1+T2+DWI+FLAIR+ADC+GRE-T2*/SWI+MRA±PWI) and DSA will be collected as DICOM format. Laboratory results will be collected in photocopies of the reports.

8.1 Screening and Inclusion

- Basic data collection: hospital name, name of patient identification, age, sex, allergy to contrast agent.
- History of present event: time of onset (time of last known well), time of arrival at the hospital, type of onset, IV thrombolysis after onset (initial time, name and dose of the drug).

- Medical history and medication before onset

Medical histories (smoking, drinking, hypertension, diabetes, dyslipidemia, cardiac arrhythmia, valvular heart disease, cardiac insufficiency, coronary atherosclerotic heart disease, peripheral arterial disease, TIA, cerebral infarction, cerebral hemorrhage, intracranial tumors), pre-stroke mRS;

Combination therapy: Antiplatelet drugs (aspirin, clopidogrel, cilostazol, prasugrel, ticagrelor, ticlopidine, etc.), anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, argatroban, etc.), statins (atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, fluvastatin, etc.).

- Physical examination

Height and weight, blood pressure, pulse, neurological evaluation (NIHSS and Glasgow scale), 12-lead electrocardiogram (ECG) .

- Emergency laboratory examinations

Emergency blood routine, emergency renal function, emergency liver function (transaminase), emergency coagulation, random blood glucose, etc.

- Imaging

A head CT is required to rule out hemorrhage and perform ASPECTS evaluation; a CTA or MRA is essential to confirm the occlusion artery; a CTP or MRI is required to calculate the infarct core volume

- All participants or his/her need to sign a written informed consent form
- Included subjects will be randomized

8.2 Data to be collected during procedure

- General anesthesia with intubation or conscious sedation with local anesthesia at start of procedure
- Procedure times: groin puncture time, time of each pass finish, time of initial flow restoration, time of successful recanalization and the end of the procedure
- eTICI score: pre-procedure and post-procedure
- Details of procedure: Accessory and adjunctive devices used (guide catheter, guidewire, intermediate catheter, microcatheter), number and type of devices for thrombectomy, number of recanalization attempt deployments, rescue procedures with medications besides thrombectomy
- Medication during the procedure: heparin, tirofiban, alteplase, urokinase.
- Intraprocedural complications: Presence of vasospasm (time of onset, vessels involved, time resolved, treatment required), evidence of clot migration or embolization, dissections, perforations, etc.

8.3 Post Treatment (Through Hospital Discharge)

A face-to-face observation will be performed at 36 hours (±12 hours) and 7 days (± 1 day)/at discharge which is earlier after randomization.

- Brain imaging performed at 36 (±12) hours after randomization: CT/CTA or MRI/MRA.
- A physical exam, as well as clinical and neurological assessments, will be completed at 36 (±12) hours and 7 (±1) days/at discharge which is earlier after randomization. Data to be collected include: vital signs (blood pressure and heart rate), relevant concomitant medications (including antiplatelet, anticoagulant, and antihypertensive agents), significant findings from clinical assessment and physical exam (i.e. all new, worsening, or improved conditions), all significant neurological findings, NIHSS Score (both), mRS (7 days or discharge only), and adverse event (AE).
- Head CT evaluation is needed at 7 days (±1 day) or at discharge whichever is earlier

- Laboratory examinations will be collected at 24 hours (±12 hours) and 7 days (± 1 day) or at discharge whichever is earlier after randomization, including: blood routine, renal function, liver function, coagulation, fasting blood glucose, etc.

8.4 Follow-up Visit at Day 30 (±3), Day 90 (±7) and 12 Months (±14 days)

These follow-up evaluations can be performed via telephone if it's not convenient for an in-person visit at the investigational site. All subjects entered into the study will undergo a standard neurological assessment by experienced physicians who are blinded to treatment assignment. Data to be collected include:

- mRS
- Patient-reported functional health status and quality of life using EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D-5L)[34]
- Relevant concomitant medications
- Significant findings from clinical assessment and physical exam (i.e. all new, worsening, or improved conditions since discharge)

8.5 Unscheduled Follow-up Visit

If an unscheduled follow-up visit occurs after randomization at the investigational site during the study, the incidence of any new or unresolved AEs will be assessed. If the visit is due to a change in neurological status, NIHSS and mRS will be completed by a certified rater.

8.6 Schedule of activities and assessments

Measurements	Baseline	36-hour (±12 hours) visit	7±1 day /at discharge visit	30-day (±3 days) visit	90 days (±7 days) visit	12-month ±14 days visit
Informed Consent	x					
Inclusion/Exclusion	x					
Randomization	x					
Demographic characteristics	x					
History of present illness	x					
Past medical history	x					
Relevant Concomitant Medications	x	x	x	x	x	x
mRS	x		x	x	x	x
NIHSS	x	x	x			
Head CT	x		x[3]			
CTA±CTP or MRI*+MRA±PWI	x[1]					
CT+CTA or MRI*+SWI+MRA		x[2]				
Carotid CTA/MRA/ultrasound		x[4]				
ASPECTS on CT	x					
Ischemic volume on CTP/DWI	x	x[5]	x[5]			
Laboratory examinations	x	x	x			
Electrocardiogram	x					
TOAST			x			
EQ-5D-5L scale				x	x	x
AE/SAE		x	x	x	x	x

[1] For all enrolled cases, CT+CTA+CTP examination was the first choice before randomization

[2] All the enrolled cases should be reviewed with multi-mode imaging 24-48 hours after randomization, and the image evaluation method should be the same as before randomization

[3] All enrolled cases should be examined by head CT at 7 days (±1 day) after randomization or at discharge which is earlier

[4] It was only applicable to patients in the standard medical treatment group who did not undergo cervical angiography prior to randomization

[5] Based on head CT or MRI, determined by the core imaging laboratory

*MRI sequence includes T1+T2+DWI+ADC+FLAIR sequence

ADC: apparent diffusion coefficient; AE: adverse event; ASPECTS: Alberta stroke program early computed tomography score; CT: computed tomography; CTA: computed tomography angiography; CTP: computed tomography perfusion; EQ-5D-5L: EuroQoL 5-Dimensions 5-Level questionnaire; FLAIR: fluid attenuated inversion recovery; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; PWI: perfusion weighted imaging; SAE: serious adverse event; SWI: susceptibility weighting imaging; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

9. Study risk pre-assessment and risk management

9.1 Monitoring of adverse events

All AEs will be managed and reported in compliance with all applicable regulations and will be included in the final Clinical Study Report (CSR).

9.2 Definitions of adverse events

9.2.1 Adverse event (AE)

Adverse Events, as long as they occur from the first visit planned in the Clinical Trial Protocol/signature of the informed consent (i.e., occurring during the washout period) to the last visit planned in the protocol, are adverse medical events or deterioration of qualifying event. AEs include symptoms (ie, nausea, chest pain), signs (ie, tachycardia, liver enlargement) and abnormal laboratory results (ie, laboratory or ECG abnormalities). AEs can be classified as serious adverse events (SAEs) and non-serious AEs.

9.2.2 Serious adverse event (SAE)

A Serious adverse event is refers to：

- Results in death, or
- Is life-threatening, or

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event

9.3 Recording of adverse events

Non-serious AE: Only some of the non-serious AEs will be collected from time of randomization throughout the treatment/follow-up periods to the Study Closure Visit. Other non-serious AEs are up to the investigator to decide whether to collect.

SAE: All SAEs will be collected and recorded.

9.4 Causal relationship between adverse events and study:

Attribution of: (1) Definite; (2) Probably; (3) Possibly; (4) Unlikely; (5) Not related; (6) Not applicable.

9.5 Obligation of the investigator regarding safety reporting

9.5.1 Adverse events

All AEs will be recorded on the corresponding page(s) in the CRF. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, outcome and his/her opinion about whether it is possible that the AE is caused by the study intervention, related to the index stroke, other cause, or intercurrent condition.

9.5.2 Serious adverse event

For SAEs, the investigator must immediately take corresponding measures:

Immediately notify the representative of the Monitoring Team, send the signed and dated corresponding pages of in the CRF to the representative of the Monitoring Team, and attach a photocopy of all examinations conducted and the examination dates. For laboratory results, include the laboratory normal ranges. The contact information (name, address and fax number) of the representative is on the Clinical Trial Protocol. These measures should be completed no later than **24 hours** after SAE.

Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly noted on all copies of source documents provided to the Sponsor.

9.5.3 Follow-up and risk management

The Investigator should take all appropriate measures to ensure the safety of the patients.

Screening of subjects should strictly follow the inclusion and exclusion criteria of the study. If an AE occurs during the study period, relevant evaluations will be performed, including blood routine examination, coagulation, creatinine, hepatic function, renal function, arterial blood gas analysis, ultrasound and computer tomography. Targeted treatment and necessary consultation should be carried out in a timely manner. When dealing with SAEs, it is important to make sure patient’s airway is clear, respiration, blood pressure and heart rate is steady.

Notably, the investigator should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc.) until the patient's condition returns to normal or stabilizes. The follow-up will continue even if the patient withdraws from the clinical trial, and the patient will be interviewed by telephone or face-to-face at the scheduled visit time. The monitoring team may request additional visits and investigations.

10. Statistical Analysis

10.1 Sample size estimation

In this study, a multicenter, open, randomized, parallel control design method was used. The primary measure of efficacy was mRS score at 90 days (±7 days) after enrollment (considered as ordered variable). According to the literature data and clinical experts' opinions, the parameters were set as follows: (1) The proportion of mRS score 0-6 in control group was 3%, 4%, 10%, 17%, 16%, 12% and 38%, respectively; (2) The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.73; (3) Two Interim analysis were considered. Adjusted level α=0.046 (two-sided) and power 1-β=0.90. (4) The randomization was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the total sample size was 452. Considering 10% attrition rate,

the final total sample size was 502 cases, 251 cases in each group.

Interim analysis will be conducted when 1/3 (168) and 2/3 (336) of patients have completed 3-month follow-up. The O'Brien-Fleming boundaries will be used at the interim analysis with a two-sided alpha of 0.0002 (stage 1), 0.0123 (stage 2) and 0.046 (stage 3, final analysis).

The PASS software (NCSS, LLC, version 11) was used to calculate the sample size.

10.2 Data collection and entry

Paper-based CRF and electronic data capture (EDC) system will be used for data collection and input. All the content required by the protocol in the system must be filled, the unfilled content should be explained, and the reason needs to be marked in the EDC system.

10.2.1 Paper-based CRF filled out by the investigator

Site investigators should use black or blue-black recording pens to fill out the paper-based CRF neatly and clearly to ensure that the data is clear and readable. If the paper-based CRF information needs to be modified, it should not be altered or overwritten. The correct information should be written next to the original information, signed and dated by the person who modified it. The clinical research monitor (Clinical Research Associate, CRA) will review the completeness and accuracy of the CRF and guide the investigator to make necessary corrections and supplements.

10.2.2 Data entry to the EDC system by CRC

After the paper-based CRF is completed, the Clinical research coordinator (CRC) will input the content of the paper CRF into the EDC system.

10.2.3 Submission to the EDC system after the approval of the investigator

The paper-based CRF is will be submitted after the investigator has approves it. After the data is submitted, all data revisions and feedback are carried out through the EDC system. If the EDC system has submitted a form that needs to be modified, contact the CRA of this center.

After the CRA opens the form, the investigator can guide the CRC to modify the data in EDC system.

10.2.4 Data monitoring and query by CRA via EDC

10.2.5 Data exportation from the EDC system

After the data from the EDC system is exported to the database, it will be proofread by the data administrator. Obvious errors will be corrected by the data administrator. Other errors or missing values will be filled in the data query form, and the query form will be sent to the participating center for solutions through email, express, telephone or WeChat.

The participating centers are responsible for correcting the data in the EDC system after verifying the original data and related information. Site investigators must answer these queries by verifying or modifying relevant information or data.

10.3 Statistical considerations

This section is an overview of the statistical considerations. It provides the general specifications for the analysis of the data to be collected and presented in the CSR. A final Statistical Analysis Plan (SAP) will be issued prior to database lockdown and before code breaking. The SAP will define all “pre-specified, planned analyses.”

All programming will be performed using SAS Version 9.4.

10.3.1 Analysis sets

(1) Full Analysis Set (FAS):

Based on the principles of the Intent-to-Treat (ITT) analysis, all randomized subjects, either treated with medication or with EVT will be included in the FAS. The primary efficacy endpoint analysis of this study will be performed on the FAS.

(2) Per Protocol Set (PPS)

The PPS is a subset that includes all subjects who were treated with the treatment

assignment to which they were randomized and there are no clinically meaningful deviations from the protocol. Severe deviations from the protocol will be finally defined during the data auditing process, including but not limited to the followings:

1) The subject is not in line with the inclusion criteria.

2) There are other treatments that potentially confound the appraisal of efficacy of the planned treatment.

3) Poor compliance.

4) Follow-up interval exceeds the required time window.

Secondary analysis will be conducted on the PPS. If its result are not consistent with that of the FAS, a detailed analysis to examine the difference(s) will be required.

(3) Safety Analysis Set (SAS)

The SAS consists of all subjects who received treatment with at least one evaluation of the safety outcome.

10.3.2 Statistical considerations

(1) Baseline characteristics comparisons

T-test or Wilcoxon rank sum test will be used for comparison between continuous variables, and Chi-squared tests, Fisher's exact test or Wilcoxon sum rank test will be used for comparison between categorical variables.

(2) Efficacy Analysis

Primary efficacy endpoint: Based on an ITT basis, an ordinal logistic regression model is used to calculate the common odds ratio between the two treatment groups. All statistics will be two-sided with $p<0.046$ considered significant.

Secondary Efficacy Analyses: Endpoints including the 90-day mRS 0-2 will be analyzed using a binary logistic regression model. The infarct core volume change from baseline will be analyzed using student t-test or Wilcoxon rank sum test as appropriate.

(3) Safety Analysis

Safety events in the two treatment groups will be described based on the SAS dataset. Logistic regression will be used to compare the differences in safety endpoints such as intracranial bleeding events between the two groups. Chi-square test and Fisher's exact test will be used to compare the differences in the incidence of AEs and SAEs between the two groups.

(4) Subgroup analysis

The mRS at 90 days will be presented for each level of the covariates listed below:

(1) Age (< 70 vs. ≥70)

(2) Weak-up stroke or not

(3) Last known well to randomization time (< 6h vs. ≥ 6h)

(4) Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16)

(5) IV thrombolysis or not

(6) Occlusion site (ICA vs. M1 segment)

(7) Ipsilateral carotid artery occlusion or not

(8) ASPECTS (< 3 points vs. ≥3 points)

(9) Infarct core volume (< 70ml vs. ≥70ml)

(10) Etiological stroke subtype (Cardiac embolism vs. large artery atherosclerosis)

10.4 Interim analysis

Interim analysis will take place when 1/3 (168 cases) and 2/3 (336 cases) have completed 3-month follow-up. The O'Brien-Fleming boundaries will be used at the interim analysis as follows:

There are no established techniques for the assessment of interim trial efficacy boundaries using an ordinal logistic regression model (proportional odds model). Instead, we will revert to a simple dichotomous analysis of the mRS score at 0-2 defined at 90 days from randomization. The Z-statistic for this analysis shall be derived from the normal approximation of the binomial distribution as an unadjusted two-sample test of proportions. For an RCT comparing two treatment groups with respect to a binary outcome and two interim analysis, corresponding

significance levels based on the O'Brien & Fleming boundary are two-sided 0.0002 (stage 1), 0.0123 (stage 2) and 0.046 (stage 3, final analysis).

With the result of interim analysis, DSMB will make the decision to continue or halt the study according to the test boundaries. The study will stop prematurely for futility if the result from the interim analysis indicate that we can't achieve an effective conclusion with the current sample size. Premature stopping for early success will be achieved if the interim analysis result has already proved the effect of intervention at significance level. Otherwise, the study will be continued until the predefined termination date. In interim analysis, the final sample size is allowed to be adjusted if the estimation of the primary outcome is drastically different from the actual data.

11. Ethical standards

11.1 Ethical standards

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice. Prior to initiating the study, each site will obtain Institutional review board (IRB) or institutional ethics committee (IEC) approval for the protocol, informed consent forms and materials used to recruit subjects. Before each subject is enrolled, the investigator is responsible for fully and comprehensively introducing the purpose, procedures and possible risks of the study to the subject or his/her agent, signing a written informed consent form, and informing the subjects that he has the right to withdraw from this study at any time. The informed consent should be kept as a clinical study document for future reference. The personal privacy and data confidentiality of subjects will be protected during the study process.

11.2 Law and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and Chinese laws and regulations, as well as any applicable guidelines.

11.3 Informed consent

The Investigator/sub-investigator should fully inform the patient of all pertinent aspects of the Clinical Trial, including the written information approved/preferred by the Ethics Committee (IRB/IEC). The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor and then submitted to the Ethics Committee (IRB/IEC) for approval.

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a patient's participation in the Clinical Trial, informed Consent Form should be signed and dated by the patient or by the patient's legal representative and by the person who conducted the informed consent discussion. A copy of the signed and dated Informed Consent Form will be provided to the patient.

11.4 Institutional review board/ Institutional ethics committee (IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and the Ethics Committee is required to forward to the Sponsor a copy of the written approval/favorable opinion signed and dated by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.), the list of voting members along with their qualification and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC). If requested, annual progress report, as well as final summary of the Clinical Trial's outcome at the end of the Clinical Trial, will also be sent to the Ethics Committee (IRB/IEC).

12. Confidentiality and publication of research findings

The principal investigator has complete intellectual property rights. The entire research process and data analysis process will strictly protect the subjects' information. Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. The trial results will be published as soon as possible after database lockdown. This trial will produce detailed data on treatment effects, medical care, and outcomes. Biostatisticians will be consulted to ensure that it is impossible to uniquely identify any participant. Diskettes with the data in comma-delimited text format, along with a data dictionary in a text file, will be sent to interested parties.

13. Study Organization

13.1 Constitution

- **The steering committee**

  - ✓ The steering committee will provide scientific and strategic direction for the trial and will have overall responsibility for its design, execution, and publication.
  - ✓ The steering committee will also be responsible for ensuring that study execution and management are of the highest quality.
  - ✓ It will approve the protocol and the operational guidelines of the trial prior to its commencement.
  - ✓ The steering committee will meet regularly by teleconference or face-to-face meetings to discuss and report the progress of the study.
  - ✓ The composition of the steering committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

Steering Committee

Member	Department	Hospital
Yongjun Wang	Department of Neurology	Beijing Tiantan Hospital, Capital Medical University

Yilong Wang	Department of Neurology	Beijing Tiantan Hospital, Capital Medical University
Liping Liu	Department of Neurology	Beijing Tiantan Hospital, Capital Medical University
David S. Liebeskind	Department of Neurology	University of California at Los Angeles
Zhongrong Miao	Department of Interventional Neuroradiology	Beijing Tiantan Hospital, Capital Medical University
Zeguang Ren	Department of Neurosurgery	The Affiliated Hospital of Guizhou Medical University
Vitor Mendes Pereira	Department of Neurosurgery, Division of Surgery	St Michael's Hospital, University of Toronto

- **Executive committee**

The executive committee is responsible for reviewing the status of the trial and available blinded data and will take appropriate actions regarding the conduct of the study. Executive Committee meetings will be organized to make major decisions. The composition of the Executive Committee and its responsibilities are described in a charter which will be finalized before the start of the trial.

- **Data safety and monitoring board (DSMB)**

The DSMB will meet regularly and monitor the study progress to ensure that the study meets the highest standards of ethics and patient safety. It is composed of Academic Members, including an independent statistician, who does not otherwise participate in the trial. A DSMB charter including membership, role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial.

Written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting.

Data safety and monitoring board

Member	**Department**	**Hospital**
Jianmin Liu	Neurovascular Center	Changhai Hospital, Naval Medical University
Chen Yao	Department of Medical Statistics	Peking University First Hospital
Kangning Chen	Department of Neurology	The Southwest Hospital of Army Medical University

- **Clinical event committee (CEC)**

Clinical events and safety endpoint will be reviewed by CEC. A CEC charter including membership, role and responsibilities will be approved before the start of the trial by the CEC and the Executive Committee.

Clinical event committee

Member	Department	Hospital
Kun Fang	Department of Neurology	Huashan Hospital, Fudan University
Bo Song	Department of Neurology	The First Affiliated Hospital of Zhengzhou University
Yi Dong	Department of Neurology	Huashan Hospital, Fudan University

- **Imaging assessment committee**

Name	Department	Hospital
Jing Jing	Tiantan Neuroimaging Center of Excellence (T-NICE)	China National Clinical Research Center for Neurological Diseases
Zhe Zhang	Tiantan Neuroimaging Center of Excellence (T-NICE)	China National Clinical Research Center for Neurological Diseases
Yingkui Zhang	Tiantan Neuroimaging Center of Excellence (T-NICE)	China National Clinical Research Center for Neurological Diseases
Wei Wu	Department of Neurology	Qilu Hospital, Shandong University

13.2 Site training and certification

Executive committee will provide training to their participating sites in Good Clinical Practice Guidelines and in some outcome assessments. Prior to initiation of patient enrollment, Site Investigators and Coordinators must complete all training programs.

The training programs that need to be completed are as follows:

(1) Study procedures

(2) ANGEL-ASPECT eligibility criteria

(3) mRS

(4) NIHSS

(5) ASPECTS

(6) iSchemaView automated RAPID® software

(7) eTICI

(8) TOAST etiology subtyping

(9) Heidelberg Bleeding Classification

(10) Collecting DICOM imaging data

Successful completion of the training program is a must before a site begin to enroll patients. The conference call will be held intermittently, and PI and key staff will be available to answer questions.

A detailed Manual of Procedures will serve as the primary document describing all study related procedures. It will serve as a guide to train clinical center personnel and will be updated periodically throughout the study on the ANGEL-ASPECT website, as needed. A system composed of members of executive committee and CRA will be implemented for the clinical centers to ask any procedural questions by phone, fax, or e-mail. The ANGEL-ASPECT executive committee and monitoring committee will formulate answers in consultation with the Steering Committee and will periodically distribute to the participating centers a set of frequently asked questions and answers.

The members of executive committee will manage and conduct site visits to ensure the integrity and validity of the data on the CRF. During the trial period, each site should be visited at least once. If there are data quality problems or recruitment problems, it should be visited as needed.

14. Study monitoring and quality assurance control

14.1 Responsibilities of the investigator(s)

The Investigator(s) should conduct the Clinical Trial in accordance with the Clinical Trial Protocol, The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator should provide reliable data and all information requested by the Protocol (with the help of the CRF, Discrepancy Resolution Form or other appropriate instruments) in an accurate and legible manner and ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint other individuals as Sub-Investigators, as he thinks appropriate. All Sub-Investigators shall be appointed and listed in a timely manner and will be supervised by the Investigator. The Investigator will provide them a copy of the Clinical Trial Protocol and all necessary information. The Sponsor is responsible for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data on the CRF.

14.2 Study monitoring

The main responsibility of the monitoring team is to help researchers to ensure that all aspects of clinical trials are ethical, scientific, professional, and standardized. According to the ICH guidelines for Good Clinical Practice (GCP), the Monitoring Team must check the CRF entries according to the source documents, except for the pre-identified.

The monitoring team will regularly contact each center through site visits or online webinar, and will send inspectors to evaluate the research progress, adherence of the investigators and patients to the research protocol and to solve urgent problems. During these inspection visits, the inspector will work together with the site-investigators. The main aspects of inspection and monitoring are as follows (not exclusive): patient's informed consent, patient recruitment and follow-up, documentation and reporting of SAEs and data quality.

15. Data retention

The double reviewed CRF and imaging data will be sent to the trial-designated data management center by CRAs. The person in charge of the data management center will check and sign the receipt form. The CRF will be kept by the research center after data entry is completed.

16. Data Security Monitoring

The data safety monitoring board (DSMB) is established to monitor the safety of participants, protect participants and ensure the integrity of the study. All AEs should be recorded, handled and tracked until they are properly resolved or stabilized. Any SAEs and unexpected events should be reported in a timely manner to the ethics committee in accordance with the relevant provisions, the competent department, the sponsor and the supervisory and administrative departments. The principal researchers should regularly review all AEs and set up meetings to assess the risks and benefits of the study if necessary. An independent data safety monitoring committee will be appointed to review safety data, evaluate the effectiveness of data monitoring, and decide whether to make new proposal.

During the clinical trial, the data of the subjects should be collected anonymously in the CRF. The subjects are identified only by the subject number and the abbreviation of the initials. Due to safety reason and administrative instructions, when the subject's identity is leaked, researchers shall share the responsibility of confidentiality. In the informed consent form, the patient allows authorized research staff, ethics committee, and the authority to refer directly to the relevant original data on the case report (such as the patient's medical file case, booking records, the original laboratory records, etc.). The above personnel shall comply with occupational confidentiality rules and must keep all patient's identity and medical information confidential.

17. Registration and Publication

17.1 Registration of study summary and results

The study representatives register a study summary in ClinicalTrials.gov (https: //clinicaltrials.gov) before the start of the study and update the summary as appropriate according to changes in the protocol or progress of the study. When the study is completed, the study representatives register a study result without delay.

17.2 Publication of study results

When the study is completed, the study database will be closed within one month after the last scheduled follow-up date of the last included patient. A manuscript which describes the study and the answer to the primary research question will be submitted to a major clinical journal within 3 months from closure of the database. The study representatives publish the results of the study after taking necessary measures (e.g., to prevent identification of specific study patients) to protect the human rights of patients and related parties or the rights and benefits of patients and related parties.

The manuscript will be shared with the financial sponsor(s) one month before submission, but the financial sponsor(s) will have no influence on its contents. Author(s) of the paper are determined by the study representatives according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http: //www.icmje.org/) by the International Committee of Medical Journal Editors (ICMJE). All authors should review and agree to the details of the paper prior to submission. The same goes for authors of conference presentations.

18. Ownership and use of data

18.1 Ownership of the data

The results, data, intellectual property rights, etc. obtained in this study belong to

the study representatives and not to the patients. Whether the intellectual property rights of the study representatives belong to the individual or to the study institution is determined by the agreement of the participating hospital.

18.2 Use of collected data

The study Steering Committee determines whether to use the data obtained in this study (hereinafter, "study data") for further study conducted by the Study representatives or sub-investigators as a secondary analysis of this study.

If the analysis is judged to be beyond the scope of secondary analysis, or if the study data is used by a person except for the study representatives or sub-investigators, the Study Steering Committee prepares a separate protocol and conducts the study after undergoing ethical review in accordance with relevant laws, regulations and ethical guidelines for medical research on human subjects.

19. Funding and conflict of interest

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20. Reference

1. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50(12):e344-e418. DOI: 10.1161/STR.0000000000000211.
2. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO)- European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. J Neurointerv Surg 2019;11(6):535-538. DOI: 10.1136/neurintsurg-2018-014568.
3. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20. DOI: 10.1056/NEJMoa1411587.

4. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18. DOI: 10.1056/NEJMoa1414792.
5. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30. DOI: 10.1056/NEJMoa1414905.
6. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306. DOI: 10.1056/NEJMoa1503780.
7. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95. DOI: 10.1056/NEJMoa1415061.
8. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med 2018;378(1):11-21. DOI: 10.1056/NEJMoa1706442.
9. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med 2018;378(8):708-718. DOI: 10.1056/NEJMoa1713973.
10. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15(11):1138-47. DOI: 10.1016/S1474-4422(16)30177-6.
11. Gautheron V, Xie Y, Tisserand M, et al. Outcome After Reperfusion Therapies in Patients With Large Baseline Diffusion-Weighted Imaging Stroke Lesions: A THRACE Trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) Subgroup Analysis. Stroke 2018;49(3):750-753. DOI: 10.1161/STROKEAHA.117.020244.
12. Deb-Chatterji M, Pinnschmidt H, Flottmann F, et al. Predictors of independent outcome of thrombectomy in stroke patients with large baseline infarcts in clinical practice: a multicenter analysis. J Neurointerv Surg 2020;12(11):1064-1068. DOI: 10.1136/neurintsurg-2019-015641.
13. Roman LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018;17(10):895-904. DOI: 10.1016/S1474-4422(18)30242-4.
14. Campbell BCV, Majoie C, Albers GW, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol 2019;18(1):46-55. DOI: 10.1016/S1474-4422(18)30314-4.
15. Sarraj A, Hassan AE, Savitz S, et al. Outcomes of Endovascular Thrombectomy vs Medical Management Alone in Patients With Large Ischemic Cores: A Secondary Analysis of the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) Study. JAMA Neurol 2019;76(10):1147-1156. DOI: 10.1001/jamaneurol.2019.2109.
16. Cagnazzo F, Derraz I, Dargazanli C, et al. Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS </=6: a meta-analysis. J Neurointerv Surg 2020;12(4):350-355. DOI: 10.1136/neurintsurg-2019-015237.
17. Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G. Triage imaging and outcome measures for large core stroke thrombectomy - a systematic review and meta-analysis. J Neurointerv Surg 2020;12(12):1172-1179. DOI: 10.1136/neurintsurg-2019-015509.
18. Rebello LC, Bouslama M, Haussen DC, et al. Endovascular Treatment for Patients With Acute Stroke Who Have a Large Ischemic Core and Large Mismatch Imaging Profile. JAMA Neurol

2017;74(1):34-40. DOI: 10.1001/jamaneurol.2016.3954.

19. Broocks G, Flottmann F, Schonfeld M, et al. Incomplete or failed thrombectomy in acute stroke patients with Alberta Stroke Program Early Computed Tomography Score 0-5 - how harmful is trying? European journal of neurology 2020;27(10):2031-2035. DOI: 10.1111/ene.14358.
20. Nicholson P, Hilditch CA, Neuhaus A, et al. Per-region interobserver agreement of Alberta Stroke Program Early CT Scores (ASPECTS). J Neurointerv Surg 2020;12(11):1069-1071. DOI: 10.1136/neurintsurg-2019-015473.
21. van Horn N, Kniep H, Broocks G, et al. ASPECTS Interobserver Agreement of 100 Investigators from the TENSION Study. Clin Neuroradiol 2021. DOI: 10.1007/s00062-020-00988-x.
22. Demeestere J, Garcia-Esperon C, Garcia-Bermejo P, et al. Evaluation of hyperacute infarct volume using ASPECTS and brain CT perfusion core volume. Neurology 2017;88(24):2248-2253. DOI: 10.1212/WNL.0000000000004028.
23. Sarraj A, Hassan AE, Grotta J, et al. Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT): A Prospective, Multicenter Cohort Study of Imaging Selection. Ann Neurol 2020;87(3):419-433. DOI: 10.1002/ana.25669.
24. Mourand I, Abergel E, Mantilla D, et al. Favorable revascularization therapy in patients with ASPECTS </= 5 on DWI in anterior circulation stroke. J Neurointerv Surg 2018;10(1):5-9. DOI: 10.1136/neurintsurg-2017-013358.
25. Inoue M, Olivot JM, Labreuche J, et al. Impact of diffusion-weighted imaging Alberta stroke program early computed tomography score on the success of endovascular reperfusion therapy. Stroke 2014;45(7):1992-8. DOI: 10.1161/STROKEAHA.114.005084.
26. Han M, Choi JW, Rim NJ, et al. Cerebral infarct volume measurements to improve patient selection for endovascular treatment. Medicine (Baltimore) 2016;95(35):e4702. DOI: 10.1097/MD.0000000000004702.
27. Manceau PF, Soize S, Gawlitza M, et al. Is there a benefit of mechanical thrombectomy in patients with large stroke (DWI-ASPECTS </= 5)? European journal of neurology 2018;25(1):105-110. DOI: 10.1111/ene.13460.
28. Broocks G, Rajput F, Hanning U, et al. Highest Lesion Growth Rates in Patients With Hyperacute Stroke. Stroke 2018:STROKEAHA118023457. DOI: 10.1161/STROKEAHA.118.023457.
29. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg 2014;6(2):83-6. DOI: 10.1136/neurintsurg-2013-010665.
30. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke; a journal of cerebral circulation 2015;46(10):2981-6. DOI: 10.1161/STROKEAHA.115.010049.
31. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke; a journal of cerebral circulation 2013;44(9):2650-63. DOI: 10.1161/STROKEAHA.113.001972.
32. Boers AM, Marquering HA, Jochem JJ, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. AJNR Am J Neuroradiol 2013;34(8):1522-7. DOI: 10.3174/ajnr.A3463.
33. Liu L, Chen W, Zhou H, et al. Chinese Stroke Association guidelines for clinical management

of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke Vasc Neurol 2020;5(2):159-176. DOI: 10.1136/svn-2020-000378.

34. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208. DOI: 10.1016/0168-8510(90)90421-9.

21. Appendix

Appendix Table 1. Modified Rankin Scale

The modified Rankin Scale (mRS) is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability. A score of 6 has been added to signify death.

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Death	Death

Appendix Table 2. Extended Treatment In Cerebral Ischemia (eTICI) Scale

eTICI grade	Short description	Long description
0	No perfusion	No antegrade flow beyond the point of occlusion
1	Limited reperfusion	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	<50% reperfusion	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
2b	≥50% and <90% reperfusion	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and its territories)
2c	≥90% reperfusion	Near complete antegrade reperfusion of the previously occluded target artery ischemic territory, except for slow flow or distal emboli in a few distal cortical vessels
3	100% reperfusion	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

MCA: middle cerebral artery; eTICI; extended treatment in cerebral ischemia scale

Appendix Table 3. National Institute of Health Stroke Scale (NIHSS)

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance. Scores range from 0 to 42, with higher scores indicating a more severe deficit. Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition
1a. Level of consciousness. The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Phasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiners not "help" the patient with verbal or non-verbal clues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hand cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.

commands. Only the first attempt is scored.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be a 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, preexisting blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0= Normal. 1= Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2= Forced deviation; or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed in this case. If there is extinction, the patient receives a 1, and the results are used to respond to item 11.	0= No visual loss. 1= Partial hemianopia. 2= Complete hemianopia. 3= Bilateral hemianopia (blind including cortical blindness)
4. Facial palsy: Ask or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1= Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2= Partial paralysis (total or near-total paralysis of lower face) 3= Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0= No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1= Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2= Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3= No effort against gravity; limb falls. 4= No movement. UN = Amputation or joint fusion: explain:

	5a = Left Arm. 5b = Right arm.
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0= No drift; leg holds 30-degree position for full 5 seconds. 1= Drift; leg falls by the end of the 5-second period but does not hit bed. 2= Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3= No effort against gravity; leg falls to bed immediately. 4= No movement. UN = Amputation or joint fusion: explain: 6a. Left Leg 6b. Right Leg.
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0= Absent. 1= Present in one limb. 2= Present in two limbs. UN = Amputation or joint fusion: explain:
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0= Normal; no sensory loss. 1= Mild-to-moderate sensory loss; patients feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2= Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg.
9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached	0= No aphasia; normal 1= Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of

list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	speech and/or comprehension, however, makes conservation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2= Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia: no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0= Normal. 1= Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood by some difficulty. 2= Severe dysarthria: patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier.
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0= No abnormality. 1= Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2= Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Appendix Table 4. EuroQoL 5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility

I have no problems in walking about	□
I have slight problems in walking about	□
I have moderate problems in walking about	□
I have severe problems in walking about	□
I am unable to walk about	□

Self-care

I have no problems washing or dressing myself	□
I have slight problems washing or dressing myself	□
I have moderate problems washing or dressing myself	□
I have severe problems washing or dressing myself	□
I am unable to wash or dress myself	□

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities	□
I have slight problems doing my usual activities	□
I have moderate problems doing my usual activities	□
I have severe problems doing my usual activities	□
I am unable to do my usual activities	□

Pain/discomfort

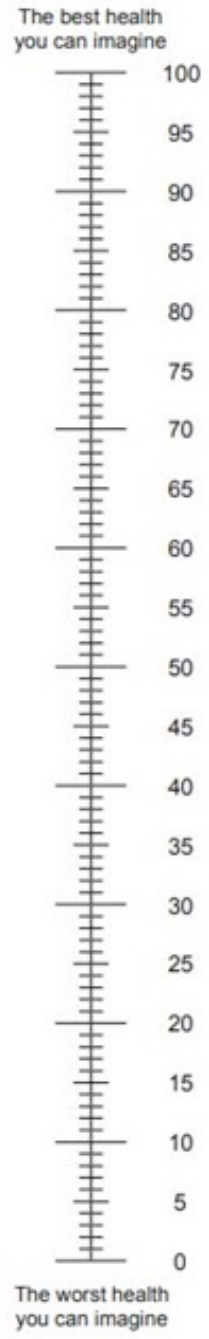
I have no pain or discomfort	□
I have slight pain or discomfort	□
I have moderate pain or discomfort	□
I have severe pain or discomfort	□
I have extreme pain or discomfort	□

Anxiety/depression

I am not anxious or depressed	□
I am slightly anxious or depressed	□
I am moderately anxious or depressed	□
I am severely anxious or depressed	□
I am extremely anxious or depressed	□

- We would like to know how good or bad your health is TOADY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALEH TOADY = ☐



Appendix Table 5. Heidelberg bleeding classification

Symptomatic intracranial hemorrhage (SICH): new intracranial hemorrhage detected by brain imaging associated with any of the items below:

1. ≥4 points decline in the total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status

2. ≥2 point decline in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of ≥4 points on the NIHSS score

Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention.

3. Absence of alternative explanation for deterioration

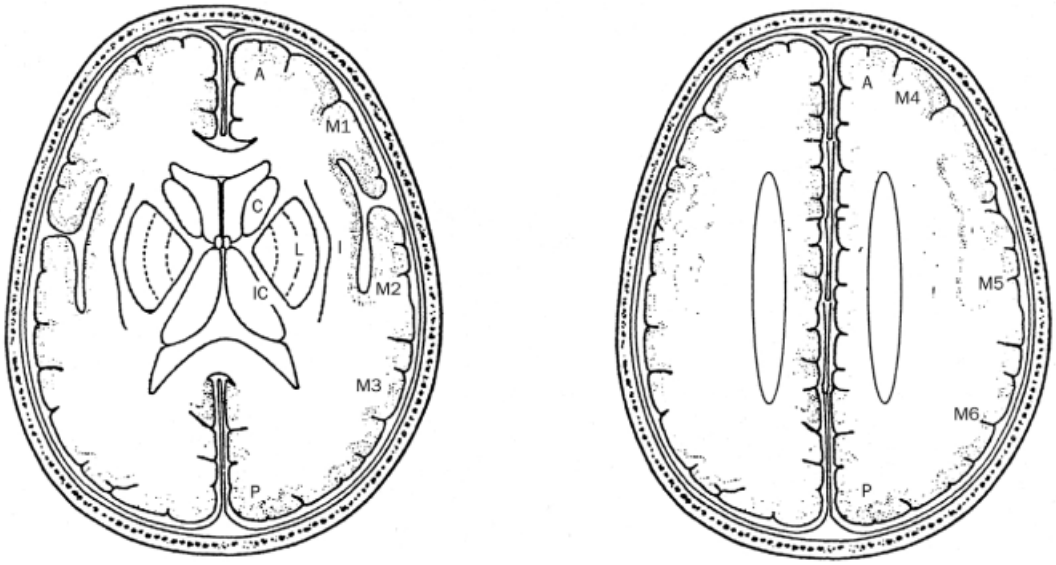
Anatomic Description of Intracranial Hemorrhages

Class	Type	Description
1	Hemorrhagic transformation of infarcted brain tissue	
1a	HI1	Scattered small petechiae, no mass effect
1b	HI2	Confluent petechiae, no mass effect
1c	PH1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2	Intracerebral hemorrhage within and beyond infarcted brain tissue	
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3	Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage	
3a		Parenchymal hematoma remote from infarcted brain tissue
3b		Intraventricular hemorrhage
3c		Subarachnoid hemorrhage
3d		Subdural hemorrhage

HI indicates hemorrhagic infarction; and PH, parenchymatous hematoma.

Appendix Table 6. Alberta Stroke Program Early CT Score (ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS) is a semiquantitative method of estimation of infarct size with non-contrast CT during the acute phase. The territory of the middle cerebral artery is allotted 10 points. 1 point is subtracted for an area of early ischaemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A normal CT scan has an ASPECTS value of 10 points. A score of 0 indicates diffuse ischaemia throughout the territory of the middle cerebral artery.



A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

Summary of changes

ANGEL-ASPECT Protocol V6.0-20200723 (original version)

ANGEL-ASPECT Protocol V7.0-20210412 (amended version)

ANGEL-ASPECT Protocol V7.1-20210518 (final version)

Version	**Date of revised**	**Changed**	**Reasons for change**
V7.0	2021/04/12	**Added Trial Registration number (cover page)**: ClinicalTrials.gov NCT04551664	Finished Trial Registration in Clinical trials.gov after the study was approved by the Ethics Committee of the hospital.
		Delete Neuroimaging Inclusion Criteria (4.1.3): "(3) Mismatch ratio on CT perfusion or MRI (Tmax>6s volume / Ischemic core volume) >1.2"	There is no need to use mismatch ratio select patients.
		Add subgroup analyses (8.2.4): "(2) Weak-up stroke or not" and "(7) Ipsilateral carotid artery occlusion or not"	To indicate more specifically the subgroup for studies by add important subgroup in the research protocol prior to data fixation.
V7.1	2021/05/18	**Extension of the Study duration (cover page) :** "August 2020 to October 2022 (enrolment completed at October 2021)" → "August 2020 to October 2023 (enrolment completed at October 2022)"	Prolonged duration because of delayed enrollment.

		Added committee tables of Study Organization (13.1): "Steering Committee, Data safety and monitoring board, Clinical event committee, Imaging assessment committee	Detailed tables of committee member.
		The parameters were refined, the interim analysis was adjusted (10.1): "(2) The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.74; (3) Two Interim analysis were considered. Adjusted level α=0.050 and power 1-β=0.90." → "(2) The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.73; (3) Two Interim analysis were considered. Adjusted level α=0.046 (two-sided) and power 1-β=0.90." **The sample size was recalculated (10.1):** "(4) The sample size was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the sample size was 219 in each group. Considering 10% attrition rate, the final total sample size was 488 cases, 244 cases in each group." → "(4) The sample size was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the total sample size was 452. Considering 10% attrition rate, the final total sample size was 502 cases, 251 cases in each group."	The parameters were refined, the interim analysis was adjusted, and the sample size was recalculated.

		Replaced Figure 1 (3.1): Study design: randomization algorithm	The figure of the study design was replaced because the sample size was recalculated
		Refined parameters (10.3.2): "All statistics will be with p<0.050 considered significant." → "All statistics will be two-sided with p<0.046 considered significant."	The parameters were refined.
		Revised interim analyses plan (10.4): "Interim analysis will take place when 1/2 (244 cases) and 3/4 (366 cases) have completed 3-month follow-up." and "corresponding significance levels based on O'Brien & Fleming boundary are 0.003 (stage 1), 0.018 (stage 2) and 0.044 (stage 3, final analysis)." → "Interim analysis will take place when 1/3 (168 cases) and 2/3 (336 cases) have completed 3-month follow-up." and "corresponding significance levels based on O'Brien & Fleming boundary are two-sided 0.0002 (stage 1), 0.0123 (stage 2) and 0.046 (stage 3, final analysis)."	Revise the interim analyses plan according to DSMB's suggestion.

Study of Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a LargE InfarCT Core: A Multicenter, Prospective, Open-Label, Blinded-Endpoint, Randomized Controlled Trial (ANGEL-ASPECT)

Statistical Analysis Plan

Principal Investigator

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Version 1.0

July 23, 2020

Table of Contents

1. Introduction

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This SAP is intended for the use of project team members and should be read in conjunction with the aforementioned protocol.

2. Study Objective

The primary objective of the study is to establish the efficacy of endovascular therapy (EVT) in Acute Anterior Circulation Large Vessel Occlusive (LVO) Patients with a large infarct core.

3. Study Endpoint(s)

Primary Efficacy Endpoints:

The 90 (±7) day modified Ranking scale.

Secondary Efficacy Endpoint:

1) 90 (±7) day mRS 0-2.

2) 90 (±7) day mRS 0-3.

3) 36h（24-48h）NIHSS 0-1 or decrease ≥10 from baseline.

4) 36h（24-48h）infarct volume change (by CT or MRI).

5) 36h（24-48h）target artery recanalization rate (by CTA or MRA).

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•Rate of symptomatic intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification).

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The primary outcome will be a shift of one or more categories (proportional odds analysis) on the modified Rankin scale determined at 90 days from randomization.
The primary hypothesis is:
H_A: Subjects in the group of best medical management plus EVT will have greater odds of showing improvement on the mRS at 90 days.

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This is a prospective, randomized, controlled, open label, blinded-endpoint (PROBE) study to compare the efficacy and safety of best medical management plus EVT compared to best medical management alone in Acute Anterior Circulation Large Vessel Occlusive (LVO) Patients with a large infarct core up to 24 hours from symptom onset or last seen well.

Patients who meet the inclusion criteria will be randomized to one of the following two treatment arms: best medical management plus EVT or best medical management alone. Endpoints in this prospective open label study will be assessed blinded to the

treatment assignment of the patient (PROBE design). This study will be conducted in approximately 50 sites in China.

Best medical management plus EVT group: Patients randomized to experimental group will receive EVT plus to best medical management. According to the pathological characteristics of patients and the judgment of researchers, the following treatment methods can be selected: Mechanical thrombectomy, angioplasty and arterial thrombolysis. Stent thrombectomy (Solitaire*, EMBOTRAP#, Trevo or Reco or other first-line stent thrombectomy systems) or aspiration (Penumbra system) is recommended as the first choice. If the recanalization is not successful, it can be replaced with balloon angioplasty or intracranial stent deployment. The need for rescue treatment is defined (including, but not limited to, a decision made by the investigator based on intraoperative conditions) as follows: three times of thrombectomy with the same thrombectomy device (stent or aspiration catheter) without successful recanalization; Target vessel was successfully recanalized and then reoccluded. Target vessel dissection or stenosis degree ≥70%, with any degree of forward flow disturbance; lumen/stent thrombus resulted in a decreased eTICI score.

Best medical management group: All the patients enrolled received standard guideline-directed medical therapy including: monitor vital signs, management of blood pressure, glucose and lipids, antithrombotic (antiplanet or anticoagulant determined by treating physician) therapy if appropriate. Intravenous thrombolysis (IVT) will be performed before EVT for patients who were eligible in compliance with the existing guideline.

The planned sample size is 488 cases, and two analyses will be conducted when the 90-day follow-up of 1/2 (244 cases) and 3/4 (366 cases) of the total sample size is completed, and the study may be terminated in advance based on clear validity or ineffectiveness. The expected duration of each subject's enrollment is approximately 1 year. Subjects will be followed with assessments at 36 (24-48) hours, hospital discharge (or 7±1 days), 30±3 days, 90±7 days and 12 months ±14 days post randomization.

A blinded core laboratory will assess baseline imaging to confirm vessel occlusion

and determine ASPECT score, 36 (24-48) hours post-randomization to assess presence of ICH, and to measure core infarct volume and determine angiographical variables such as final reperfusion status and residual stenosis.

6. Sample size estimates

In this study, a multicenter, open, randomized, parallel control design method was used. The primary measure of efficacy was mRS score at 90±7 days after enrollment (considered as ordered variable). According to the literature data and clinical experts' opinions, the parameters were set as follows: (1) The proportion of mRS score 0-6 in control group was 3%, 4%, 10%, 17%, 16%, 12% and 38%, respectively; (2) The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.74; (3) Two Interim analysis were considered. Adjusted level α=0.05 and power 1-β=0.90. (4) The sample size was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the total sample size was 438. Considering 10% attrition rate, the final total sample size was 488 cases, 244 cases in each group.

Interim analysis will take place when 1/2 (244 cases) and 3/4 (366 cases) have completed 3-month follow-up. O'Brien-Fleming boundaries will be used at the interim analysis as follows:

There are no established techniques for the assessment of interim trial efficacy boundaries using an ordinal logistic regression model (proportional odds model). Instead, we will revert to a simple dichotomous analysis of the mRS score at 0-2 defined at 90 days from randomization. The Z-statistic for this analysis shall be derived from the normal approximation of the binomial distribution as an unadjusted two-sample test of proportions. For an RCT comparing two treatment groups with respect to a binary outcome and two interim analysis, corresponding significance levels based on O'Brien & Fleming boundary are two-sided 0.003 (stage 1), 0.018 (stage 2) and 0.044 (stage 3, final analysis).

With the result of interim analysis, DSMB will make the decision to continue or

halt the study according to the test boundaries. The study will stop prematurely for futility if the result from the interim analysis indicate that we can't achieve an effective conclusion with the current sample size. Premature stopping for early success will be achieved if the interim analysis result has proven the effect of intervention at significance level. Otherwise, the study will be continued until the predefined termination date. In interim analysis, the final sample size is allowed to be adjusted if the estimation of the primary outcome is drastically different from the actual data.

7. Analysis populations

Full Analysis Set (FAS)

Based on the principles of Intention-to-Treat analysis (ITT), all randomized subjects, either treated with medication or with EVT will be included in the full analysis set. The primary effectiveness endpoint analysis of this study will be performed on the FAS.

Per Protocol Set (PPS)

The PPS is a subset that includes all subjects who were treated with the treatment to which they were randomized and there are no clinically meaningful deviations from the protocol. Severe derivations from the protocol will be finally defined during the data auditing process, including but not limited to the followings:

1) The subject is not in line with the inclusion criteria.
2) There exist other treatments that potentially confound the appraisal of efficacy of the planned treatment.
3) Poor compliance.
4) Follow-up interval exceeds the required time window.

Secondary analysis will be conducted on the PPS, whenever its result is not consistent with the one from the FAS, a detailed analysis of the difference is needed.

Safety Analysis Set (SAS)

The safety analysis set consists of all subjects who received treatment with at least one time evaluation of safety outcome.

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The treatment comparison of interest in this study is to assess the safety and efficacy of best medical management plus EVT compared to best medical management alone in patients with AIS due to LVO in anterior circulation up to 24 hours from symptom onset or last seen well.

9. General considerations for data analyses

All analyses will be performed using SAS Version 9.4. All analysis output will use the treatment group naming of best medical management plus EVT group and best medical management group. All statistics were two sided with a $P<0.05$ considered significant.

Examination of Subgroups

The extent to which the treatment effect of improvement in modified Ranking scale varies across levels of each subgroup will be assessed through interaction tests.

Multiple Comparisons and Multiplicity

A single primary efficacy variable has been defined for this study, with all other efficacy variables identified as secondary or other. Similarly, only one treatment comparison is of interest in the study and therefore there are no requirements to adjust for multiple comparisons or multiple endpoints within this study.

10. Data handling conventions

Premature Withdrawal and Missing Data

If any subject withdraws prematurely from the study (prior to the final visit D90±7 days assessment), they are required to complete the withdrawal visit in the CRF. The reasons for withdrawal will be presented in a summary table. For the purposes of summaries and analysis of clinic visit data, this visit will be assigned to the next scheduled clinic visit for that subject, regardless of whether the date falls within the next visit window.

Subjects who withdraw before the end of the study, but who do provide at least one post-baseline measure for a particular endpoint, will be included in the analysis. Subjects who do not attend any visits after randomization will be excluded from analysis of any endpoint, as no post-baseline data will be available.

Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid (e.g., deemed incompatible with life by Medical Monitor and/or deemed invalid by the DSMB).

Efforts will be undertaken at study sites to reduce the amount of missing data. Due to the severity of the condition and the short 90-day follow-up period, very little loss to follow-up is anticipated. For the primary efficacy endpoint, complete data will be used and missing data will not be imputed in the main analysis. Also, sensitivity analyses with missing data imputed by LOCF (Last Observation Carry Forward) and WCCF (Worst Case Carry Forward) methods will be undertaken to explore the effect of missing data on the endpoint and test the robustness of the estimate.

Event Rates

The number of events should be recorded in detail and showing the event rate in 90 days of each treatment group in summary statement.

The event rate for each treatment group will be calculated as: the sum of number of event for all the patients / the sum of number of treatment periods for all the patients.

11.Study Population

Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the Per Protocol population will be listed, and the total number of subjects attending each clinic visit will also be summarized by treatment group.

The number of subjects randomized, completed and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.

A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or randomized into the trial.

Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol.

Subjects who commit protocol violations will be included in the FAS Population but excluded from the Per Protocol Population. These protocol violations will be shown in a listing. Subjects can either be full or partial protocol violators. A full protocol violator is completely excluded from the Per Protocol Population. A partial protocol violator has only some data excluded. For subjects who violated the protocol during the treatment period due to unpermitted changes in the medication or prohibited concurrent medication, the analysis will only use data recorded prior to the violation. For all violations which reference the treatment period, the treatment start date will be used as the reference date.

A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from

the Per-Protocol population will be agreed by the study team.

Demographic and Baseline Characteristics

The following demographic information will be listed and summarized for subjects in each treatment group: age, sex, medical history, smoking history, weak-up stroke, randomization time, NIHSS score, intravenous thrombolysis, occlusion site, ipsilateral carotid artery occlusion, ASPECT score, infarct core volume and stroke subtype.

The continuous data followed normal distribution will be presented as mean and standard deviation, and the continuous data followed skewed distribution will be presented as median and interquartile range; categorical data will be presented as n(%). T-test or Wilcoxon rank sum test will be used for comparison between continuous variables, and Chi-squared tests, Fisher's exact test or Wilcoxon sum rank test will be used for comparison between categorical variables.

12. Efficacy Analyses

Primary Efficacy Analysis

The primary endpoint is the modified Ranking scale at 90-day. FAS will be the primary population for efficacy analyses. PPS will be used as secondary population for the efficacy analyses. If the results in the PPS population are inconsistent with the FAS population, detailed analysis of the inconsistent results is required.

Main Model

Based on an intention-to-treat basis, an ordinal logistic regression model with site as a random effect will be used to calculate the common odds ratio between the two treatment groups. If the proportional odds assumption for ordinal logistic regression were not satisfied, the Wilcoxon-Mann-Whitney generalized odds ratio will be calculated using assumption-free ordinal analysis. All statistics will be two-sided with $p<0.046$ considered significant.

Interactions with Subgroups

Summary tables will be produced for the predefined subgroups and interactions between treatment and these subgroups will be investigated, using an ordinal logistic regression model. A separate model will be used for each interaction to determine its significance. This will also be presented graphically on a forest plot.

The predefined subgroups including:

- Age (< 75 vs. ≥75)
- Last known well to randomization time (< 6h vs. ≥ 6h)
- Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16)
- Intravenous thrombolysis or not
- Occlusion site (ICA vs. M1 segment)
- ASPECT score (< 3 points vs. ≥3 points)
- Infarct core volume (< 70ml vs. ≥70ml)
- Etiological stroke subtype (cardiac embolism vs. large artery atherosclerosis)

Secondary Efficacy Analyses

90-day mRS 0-2

The proportion of 90-day mRS 0-2 will be analyzed using a binary logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

90-day mRS 0-3

The proportion of 90-day mRS 0-3 will be analyzed using a binary logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

36h（24-48h）NIHSS 0-1 or decrease ≥10 from baseline

The proportion of 36h（24-48h）NIHSS 0-1 or decrease ≥10 points from baseline will be analyzed using a binary logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

36h（24-48h）infarct volume change (by CT or MRI)

The change of 36h（24-48h）infarct volume change (by CT or MRI) will be analyzed using student t-test or Wilcoxon rank sum test as appropriate.

36h（24-48h）target artery recanalization rate (by CTA or MRA)

The 36h（24-48h）target artery recanalization rate (by CTA or MRA) will be analyzed using a logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

13.Safety Analyses

All analyses of safety data will be carried out using the safety set (SS) population.

Primary Safety Endpoints

Rate of symptomatic intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification).

Secondary Safety Endpoints

All-cause mortality within 90 days.

Rate of any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification).

Rate of decompressive hemicraniectomy during hospitalization.

For most bleeding events, the binary logistic model with site as a random effect will be used to compare the odds ratio between the two treatments, or Poisson regression or negative binomial regression which are more appropriate for the analysis of rare event. For all-cause mortality within 90 days, the Cox proportional hazards model with site as a random effect will be used to compare the hazard ratio between the two treatments.

Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary (Version 6.0 or a later release) and grouped by system organ class (as detailed in the study protocol). Separate data display listings and summaries will be presented for adverse events that start prior to first dose of study medication (pre-treatment), whilst on study medication

(during treatment) and after the last dose of study medication (post-treatment).

Within each treatment group, the number and percentage of subjects experiencing an AE will be summarized by system organ class and preferred term and Fisher's Exact test will be used to compare the number of each grouped AE event between treatment groups. In addition, a separate summary will be provided for AEs experienced by more than 5% of subjects in either of the treatment groups.

Serious Adverse Events

Summary tables and data displays will be provided for serious adverse events (as detailed in the study protocol). In addition, all deaths and serious AE's will be documented in a case narrative format in the clinical study report.

The number of adverse events or serious adverse events occurring over the treatment period will be summarized and Fisher's Exact test will be used to compare between treatment groups.

14. References

1. De Mets DL, Furberg CD, Friedman LM. Data monitoring in clinical trials. New York: Springer; 2006.
2. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. New York: Chapman & Hall; 2000.
3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-103

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Principal Investigator

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Version 2.0

May 18, 2021

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10. Data handling conventions

Premature Withdrawal and Missing Data

If any subject withdraws prematurely from the study (prior to the final visit D90±7 days assessment), they are required to complete the withdrawal visit in the CRF. The reasons for withdrawal will be presented in a summary table. For the purposes of summaries and analysis of clinic visit data, this visit will be assigned to the next scheduled clinic visit for that subject, regardless of whether the date falls within the next visit window.

Subjects who withdraw before the end of the study, but who do provide at least one post-baseline measure for a particular endpoint, will be included in the analysis. Subjects who do not attend any visits after randomization will be excluded from analysis of any endpoint, as no post-baseline data will be available.

Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid (e.g., deemed incompatible with life by Medical Monitor and/or deemed invalid by the DSMB).

Efforts will be undertaken at study sites to reduce the amount of missing data. Due to the severity of the condition and the short 90-day follow-up period, very little loss to follow-up is anticipated. For the primary efficacy endpoint, complete data will be used and missing data will not be imputed in the main analysis. Also, sensitivity analyses with missing data imputed by LOCF (Last Observation Carry Forward) and WCCF (Worst Case Carry Forward) methods will be undertaken to explore the effect of missing data on the endpoint and test the robustness of the estimate.

Event Rates

The number of events should be recorded in detail and showing the event rate in 90 days of each treatment group in summary statement.

The event rate for each treatment group will be calculated as: the sum of number of event for all the patients / the sum of number of treatment periods for all the patients.

11.Study Population

Disposition of Subjects

The number of subjects in each analysis population will be presented, subjects to be excluded from the Per Protocol population will be listed, and the total number of subjects attending each clinic visit will also be summarized by treatment group.

The number of subjects randomized, completed and prematurely withdrawn from the study will be presented for each treatment group. The primary reasons for withdrawal both prior to and post randomization will also be presented.

A data display listing and summary of deviations from the inclusion/exclusion criteria will be presented for all subjects who were either entered or randomized into the trial.

Protocol Deviations

Subject data will be examined for evidence of protocol violators in order to assess how well the protocol was followed. Inclusion and exclusion criteria are detailed in the study protocol.

Subjects who commit protocol violations will be included in the FAS Population but excluded from the Per Protocol Population. These protocol violations will be shown in a listing. Subjects can either be full or partial protocol violators. A full protocol violator is completely excluded from the Per Protocol Population. A partial protocol violator has only some data excluded. For subjects who violated the protocol during the treatment period due to unpermitted changes in the medication or prohibited concurrent medication, the analysis will only use data recorded prior to the violation. For all violations which reference the treatment period, the treatment start date will be used as the reference date.

A listing of all possible protocol violators will be produced for clinical review. The final list of subjects who are protocol violators and are therefore excluded from

the Per-Protocol population will be agreed by the study team.

Demographic and Baseline Characteristics

The following demographic information will be listed and summarized for subjects in each treatment group: age, sex, medical history, smoking history, weak-up stroke, randomization time, NIHSS score, intravenous thrombolysis, occlusion site, ipsilateral carotid artery occlusion, ASPECT score, infarct core volume and stroke subtype.

The continuous data followed normal distribution will be presented as mean and standard deviation, and the continuous data followed skewed distribution will be presented as median and interquartile range; categorical data will be presented as n(%). T-test or Wilcoxon rank sum test will be used for comparison between continuous variables, and Chi-squared tests, Fisher's exact test or Wilcoxon sum rank test will be used for comparison between categorical variables.

12. Efficacy Analyses

Primary Efficacy Analysis

The primary endpoint is the modified Ranking scale at 90-day. FAS will be the primary population for efficacy analyses. PPS will be used as secondary population for the efficacy analyses. If the results in the PPS population are inconsistent with the FAS population, detailed analysis of the inconsistent results is required.

Main Model

Based on an intention-to-treat basis, an ordinal logistic regression model with site as a random effect will be used to calculate the common odds ratio between the two treatment groups. If the proportional odds assumption for ordinal logistic regression were not satisfied, the Wilcoxon-Mann-Whitney generalized odds ratio will be calculated using assumption-free ordinal analysis. All statistics will be two-sided with $p<0.046$ considered significant.

Interactions with Subgroups

Summary tables will be produced for the predefined subgroups and interactions between treatment and these subgroups will be investigated, using an ordinal logistic regression model. A separate model will be used for each interaction to determine its significance. This will also be presented graphically on a forest plot.

The predefined subgroups including:

- Age (< 75 vs. ≥75)
- Weak-up stroke or not
- Last known well to randomization time (< 6h vs. ≥ 6h)
- Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16)
- Intravenous thrombolysis or not
- Occlusion site (ICA vs. M1 segment)
- Ipsilateral carotid artery occlusion or not
- ASPECT score (< 3 points vs. ≥3 points)
- Infarct core volume (< 70ml vs. ≥70ml)
- Etiological stroke subtype (cardiac embolism vs. large artery atherosclerosis)

Secondary Efficacy Analyses

90-day mRS 0-2

The proportion of 90-day mRS 0-2 will be analyzed using a binary logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

90-day mRS 0-3

The proportion of 90-day mRS 0-3 will be analyzed using a binary logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

36h（24-48h）NIHSS 0-1 or decrease ≥10 from baseline

The proportion of 36h（24-48h）NIHSS 0-1 or decrease ≥10 points from baseline will be analyzed using a binary logistic regression model with site as a random effect. The

odds ratio with 95% CI will be reported.

36h（24-48h）infarct volume change (by CT or MRI)

The change of 36h（24-48h）infarct volume change (by CT or MRI) will be analyzed using student t-test or Wilcoxon rank sum test as appropriate.

36h（24-48h）target artery recanalization rate (by CTA or MRA)

The 36h（24-48h）target artery recanalization rate (by CTA or MRA) will be analyzed using a logistic regression model with site as a random effect. The odds ratio with 95% CI will be reported.

13.Safety Analyses

All analyses of safety data will be carried out using the safety set (SS) population.

Primary Safety Endpoints

Rate of symptomatic intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification).

Secondary Safety Endpoints

All-cause mortality within 90 days.

Rate of any intracranial hemorrhage within 48 hours from randomization (Heidelberg Bleeding Classification).

Rate of decompressive hemicraniectomy during hospitalization.

For most bleeding events, the binary logistic model with site as a random effect will be used to compare the odds ratio between the two treatments, or Poisson regression or negative binomial regression which are more appropriate for the analysis of rare event. For all-cause mortality within 90 days, the Cox proportional hazards model with site as a random effect will be used to compare the hazard ratio between the two treatments.

Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary (Version 6.0 or a later release) and grouped by system organ class (as detailed in the study protocol).

Separate data display listings and summaries will be presented for adverse events that start prior to first dose of study medication (pre-treatment), whilst on study medication (during treatment) and after the last dose of study medication (post-treatment).

Within each treatment group, the number and percentage of subjects experiencing an AE will be summarized by system organ class and preferred term and Fisher's Exact test will be used to compare the number of each grouped AE event between treatment groups. In addition, a separate summary will be provided for AEs experienced by more than 5% of subjects in either of the treatment groups.

Serious Adverse Events

Summary tables and data displays will be provided for serious adverse events (as detailed in the study protocol). In addition, all deaths and serious AE's will be documented in a case narrative format in the clinical study report.

The number of adverse events or serious adverse events occurring over the treatment period will be summarized and Fisher's Exact test will be used to compare between treatment groups.

14. References

1. De Mets DL, Furberg CD, Friedman LM. Data monitoring in clinical trials. New York: Springer; 2006.
2. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. New York: Chapman & Hall; 2000.
3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-1030.

Revisions to previous SAP version

SAP version 1.0	Changes in SAP version 2.0
5. Design The planned sample size is 488 cases, and two analyses will be conducted when the 90-day follow-up of 1/2 (244 cases) and 3/4 (366 cases) of the total sample size is completed.	5. Design The planned sample size is 502 cases, and two analyses will be conducted when the 90-day follow-up of 1/3 (168 cases) and 2/3 (336 cases) of the total sample size is completed.
6. Sample size estimates …The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.74; (3) Two Interim analysis were considered. Adjusted level α=0.05 and power 1-β=0.90. (4) The sample size was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the total sample size was 438. Considering 10% attrition rate, the final total sample size was 488 cases, 244 cases in each group. Interim analysis will take place when 1/2 (244 cases) and 3/4 (366 cases) have completed 3-month follow-up. O'Brien-Fleming boundaries will be used at the interim analysis as follows: … For an RCT comparing two treatment groups with respect to a binary outcome and two interim analysis, corresponding significance levels based on O'Brien & Fleming boundary are two-sided 0.003 (stage 1), 0.018 (stage 2) and 0.044 (stage 3, final analysis).	6. Sample size estimates …The average treatment effect of EVT improved the outcome with the common OR value for improvement of mRS reached 1.73; (3) Two Interim analysis were considered. Adjusted level α=0.046 (two-sided) and power 1-β=0.90. (4) The sample size was allocated to the intervention group and the control group in a 1:1 ratio. Based on these parameters, the total sample size was 452. Considering 10% attrition rate, the final total sample size was 502 cases, 251 cases in each group. Interim analysis will take place when 1/3 (18 cases) and 2/3 (336 cases) have completed 3-month follow-up. O'Brien-Fleming boundaries will be used at the interim analysis as follows: … For an RCT comparing two treatment groups with respect to a binary outcome and two interim analysis, corresponding significance levels based on O'Brien & Fleming boundary are two-sided 0.0002 (stage 1), 0.0123 (stage 2) and 0.046 (stage 3,

	final analysis).
The predefined subgroups including: ・Age (< 75 vs. ≥75) ・Last known well to randomization time (< 6h vs. ≥ 6h) ・Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16) ・Intravenous thrombolysis or not ・Occlusion site (ICA vs. M1 segment) ・ASPECT score (< 3 points vs. ≥3 points) ・Infarct core volume (< 70ml vs. ≥70ml) ・Etiological stroke subtype (cardiac embolism vs. large artery atherosclerosis)	The predefined subgroups including: ・Age (< 75 vs. ≥75) ・Weak-up stroke or not ・Last known well to randomization time (< 6h vs. ≥ 6h) ・Stroke severity before randomization (NIHSS<16 vs. NIHSS≥16) ・Intravenous thrombolysis or not ・Occlusion site (ICA vs. M1 segment) ・Ipsilateral carotid artery occlusion or not ・ASPECT score (< 3 points vs. ≥3 points) ・Infarct core volume (< 70ml vs. ≥70ml) ・Etiological stroke subtype (cardiac embolism vs. large artery atherosclerosis)

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Manuscript title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial

Corresponding author: Prof. Liping Liu or Prof. Zhongrong Miao or Dr. Xinyi Leng

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Authors' contributions

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XL, ZM and LL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LZ, XN, YP, XL, LL. Acquisition, analysis, or interpretation of data: LZ, MW, XL, WD, ZZ, YW, JL, GM, XH. Drafting of the manuscript: LZ, XL. Critical revision of the manuscript for important intellectual content: TNN, MW, ZY, TWL, ZM, LL. Statistical analysis: LZ, MW, YP. Obtained funding: ZM, LL. Supervision: TWL, XL, ZM, LL. ZM and LL had access to the database and LL had final responsibility for the decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Corresponding author declaration

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Manuscript number (if known): eclinm-D-24-00250

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Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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Time frame: past 36 months			
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3	Royalties or licenses	None	
4	Consulting fees	None	
5		None	

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6	Payment for expert testimony	____None	
7	Support for attending meetings and/or travel	____None	
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11	Stock or stock options	____None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	____None	
13	Other financial or non-financial interests	____None	

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Zhe Zhang
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Jingyi Liu
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Yufei Wei
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Miao Wen
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Zhonghua Yang
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Thomas W Leung
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Gaoting Ma
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Xiaochuan Huo
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Yuesong Pan
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Thanh N Nguyen
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Xinyi Leng
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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Date: Mar 22, 2024
Your Name: Zhongrong Miao
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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__X__ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: Mar 22, 2024
Your Name: Liping Liu
Manuscript Title: Endovascular therapy in acute ischemic stroke with large infarction with matched or mismatched clinical-radiological severities: a post-hoc analysis of the ANGEL-ASPECT trial
Manuscript number (if known): eclinm-D-24-00250

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