SVN Stroke & Vascular Neurology

Endovascular therapy in acute anterior circulation large vessel occlusive patients with a large infarct core (ANGEL-ASPECT): protocol of a multicentre randomised trial

Xiaochuan Huo ,[1,2] Gaoting Ma ,[1,2] Xuelei Zhang,[3] Yuesong Pan ,[2,4] Xu Tong ,[1,2] Dapeng Sun ,[1,2] Liping Liu ,[2,4] Yilong Wang ,[2,4] David S Liebeskind ,[5] Yongjun Wang,[2,4] Vitor Mendes Pereira,[6] Zeguang Ren ,[7] Zhongrong Miao[1,2]

To cite: Huo X, Ma G, Zhang X, *et al*. Endovascular therapy in acute anterior circulation large vessel occlusive patients with a large infarct core (ANGEL-ASPECT): protocol of a multicentre randomised trial. *Stroke & Vascular Neurology* 2022;**0**. doi:10.1136/svn-2022-001865

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2022-001865).

XH and GM contributed equally.

Received 12 July 2022
Accepted 7 September 2022

For numbered affiliations see end of article.

Correspondence to
Dr Zhongrong Miao; zhongrongm@163.com

ABSTRACT

Background The benefit of stroke thrombectomy for large infarct core still lacks robust randomised controlled studies.

Aim To demonstrate the design of a clinical trial on endovascular therapy for acute anterior circulation large vessel occlusion (LVO) patients with large infarct core volume.

Design ANGEL-ASPECT is a multicentre, prospective, randomised, open-label, blinded End-point trial to evaluate whether best medical management (BMM) combined with endovascular therapy improves neurological functional outcomes as compared with BMM alone in acute LVO patients with Alberta Stroke Program Early CT Score (ASPECTS) of 3–5 on non-contrast CT or infarct core volume range of 70–100 mL (defined as rCBF <30% on CT perfusion or ADC <620 on MRI) up to 24 hours from symptom onset or last seen well.

Study outcomes The primary efficacy outcome is 90 (±7) days modified Rankin Scale. Symptomatic intracranial haemorrhage within 48 hours from randomisation is the primary safety outcome.

Discussion The ANGEL-ASPECT trial will screen patients with large infarct core (ASPECTS 3–5 or 70–100 mL) through image evaluation criteria within 24 hours and explore the efficacy and safety of endovascular therapy compared with BMM.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Whether thrombectomy is benefit for patients with large infarct core is still controversial.

WHAT THIS STUDY ADDS

⇒ This protocol demonstrated the rationale and design of ANGEL-ASPECT.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ ANGEL-ASPECT trial will produce objective data on whether best medical management combined with endovascular therapy improves neurological outcome for acute large vessel occlusion patients with large infarct core compared with best medical management alone.

INTRODUCTION AND RATIONALE

Endovascular therapy (EVT) has now become a standard strategy for patients with acute large vascular occlusion. However, large infarct core volume is excluded from the therapy guideline of patient with acute stroke.[1] Currently, the approved imaging inclusion criteria for the selection of patient is limited to Alberta Stroke Program Early CT Scores (ASPECTS) score ≥6 within 6 hours or the criteria set by the studies of diffusion-weighted imaging (DWI) or CT perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) and The Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke (DEFUSE 3) criteria in 6–16 or 24 hours.[1 2] However, whether thrombectomy is of benefit for patients out of the guidelines is still controversial.[3 4]

HERMES collaboration found that EVT showed benefit compared with control group for patients with ASPECTS 0–4[5] and core volume ≥70 mL defined by CTP, or DWI MRI.[6] The 90 day modified Rankin Scale (mRS) of 0–2 was 25% in EVT group vs 14% in control for patients with an ASPECT score of 0–4.[5]

Many studies showed benefit of thrombectomy for large infarct core volume defined by low ASPECTS or large CTP or ADC volume.[3 7–10] Recently, the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT)[11] showed patients with large infarct core (ASPECTS 3–5)

benefits form EVT compared with medical management alone but EVT is associated with more intracranial haemorrhages (ICH).

The benefit is obvious when narrowed the scope to low ASPECTS 3–5 or large infarct core volume 70–100 mL. The Optimising Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) trial showed that large infarct core patients may benefit from endovascular treatment, especially when treated in early time window and with a infarct core volume within 100 mL. HERMES study only had small percent of patients with a infarct core volumes for more than 100 mL.[7] Based on these evidences, we designed the combination imaging selection criteria for ANGEL-ASPECT and defined large infarct core volume using low ASPECTS or large CTP or ADC volume. ANGEL-ASPECT trial will include patients with non-contrast CT (NCCT) ASPECTS 3–5 and perfusion core volume 70–100 mL when ASPECTS <3 / > 5 (6–24 hours). This combination imaging inclusion criteria allows us to include the maximum of patients with a potential benefit large infarct core for whom EVT is not recommended with level 1 evidence under current guidelines.

METHODS

Hypothesis

Best medical management (BMM) combined with EVT might be superior to BMM alone in acute anterior circulation large vessel occlusive (LVO) patients with a large infarct core volume.

Design and patient population

ANGEL-ASPECT study is a multicentred, prospective, randomised, open-label, blinded End-point (PROBE) trial. Patients with acute LVO of middle cerebral artery (M1 segment), and/or distal internal carotid artery (ICA) (intracranial segment), determined by CT angiography (CTA) or MR angiography (MRA), and who meet eligibility criteria and do not meet exclusion criteria will be considered for enrolment at 46 sites in China (online supplemental table 1). Box 1 lists the inclusion criteria and exclusion criteria.

Randomisation

The random code will be generated through a central network randomisation system with 24 hours real-time randomisation online based on the simple randomisation method. The researcher in each centre will obtain the random code from the central network randomisation system according to the enrolment order, and patients who meet the inclusion criteria and obtain informed consent will be randomly assigned to the following treatment groups in a 1:1 ratio (figure 1):

- BMM plus EVT group: patients will receive EVT on the basis of BMM, with stent retriever thrombectomy or contact aspiration thrombectomy preferred for EVT.
- BMM group: patients will receive the BMM alone.

Box 1 Summary of inclusion and exclusion criteria.

Inclusion criteria

Centre inclusion criteria

(1) Equipped with emergency department and neurology department for patients who had a stroke.

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

(3) Capable of endovascular treatment and intravenous thrombolysis for acute ischaemic stroke patients.

Clinical inclusion criteria:

(1) Age 18–80 years.

(2) Presenting with symptoms consistent with acute ischaemic stroke.

(3) Prestroke modified Rankin Scale score 0–1.

(4) National Institute of Health Stroke Scale (NIHSS) score 6–30 at the time of randomisation.

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

(6) Informed consent signed.

Neuroimaging inclusion criteria:

(1) CT angiography or MR angiography proved occlusion of internal carotid artery terminal or M1 segment of middle cerebral artery.

(2) Combination of non-contrast CT (NCCT) ASPECTS and perfusion core volume when ASPECTS <3 or > 5 (6–24 hours). Imaging evidence of low ASPECTS (based on NCCT) or large infarct Core (defined as rCBF <30% on CT perfusion or ADC <620 on MRI) filling one of the following criteria:

(1) ASPECTS 3–5.

(2) ASPECTS>5 (6–24 hours) with infarct core volume 70–100 mL, to catch the patients who may have true large infarct core but missed by misinterpreted upper limit ASPECTS.

(3) ASPECTS <3 with infarct core volume 70–100 mL, to catch the patients who may have true large volume core with range of ASPECTS 3–5 but missed by misinterpreted lower limit ASPECTS.

Exclusion criteria

Centre exclusion criteria

(1) Centres in which the number of acute ischaemic 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 mm Hg or diastolic blood pressure >110 mm Hg).

(4) Known haemorrhagic tendency (including but not limited to): baseline platelet count $< 100\times10^9$/L/L; heparin was administered within 48 hours with APTT ≥35 s; on anticoagulant therapy with warfarin and international normalised 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 enrolment).

(5) Parenchymal organ surgery and biopsy were performed in the past 1 month.

(6) Any active bleeding or recent bleeding (gastrointestinal bleeding, urinary bleeding, etc) in the past 1 month.

(7) Undergoing haemodialysis or peritoneal dialysis; known severe renal insufficiency with glomerular filtration rate <30 mL/min or serum creatinine >220 mmol/L (2.5 mg/dL mg/dL).

Continued

Box 1 Continued

(8) Brain tumour (with mass effect).

(9) The expected survival time is less than 1 year year (such as complicated with malignant tumour, serious heart and lung diseases).

(10) Participation in other interventional randomised clinical trials that may confound 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).

Specific neuroimaging exclusion criteria

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

(2) Evidence of acute intracranial haemorrhage.

(3) Acute bilateral strokes or multiple intracranial vessels occlusions.

Intervention

Endovascular therapy

When the patient's condition permits, local anaesthesia is the first choice for rapid initiation of arterial puncture and EVT. 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 anaesthesia should be used. Return to the neurointensive care unit with intubation or not should be determined according to the surgical results.

Systemic heparinisation 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 and other first-line stent retriever systems) and contact aspiration (Penumbra aspiration system and other first-line aspiration system) are recommended as the first choice for thrombectomy.

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

Best medical management

All enrolled patients should receive BMM in accordance with the recommendation of Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders.[12] This includes intravenous thrombolysis therapy for patients meeting the guidelines. Patients who meet the criteria should receive intravenous thrombolysis therapy according to the guidelines, while informed consent and screening are still available for patients who have completed intravenous thrombolysis. Patients who plan to undergo or are undergoing intravenous thrombolysis therapy will continue or terminate intravenous thrombolysis therapy after enrolment according to the investigator's judgement. Patients who had completed intravenous thrombolysis prior to randomisation were also eligible for enrolment in this trial. All patients are recorded with the name, dosage, and time of intravenous thrombolysis drugs in detail. Antiplatelet agents are not recommended within 24 hours after intravenous thrombolysis unless the patient has undergone balloon dilatation or stent implantation, at which time the antithrombotic strategy is determined by the onsite investigator. Non-intravenous thrombolysis patients will be treated with aspirin, unless an indication for early anticoagulation is present.

Imaging protocol

Baseline imaging

All investigators were trained on the imaging protocol and use of RAPID software, and participated in the network training, simulation test and examination of NCCT-ASPECTS before enrolment. ASPECTS training and test is conducted through the online training system of the trial website (http://angel-aspect.org). Those who pass the exam (>80 points) will obtain the ASPECTS assessment qualification certificate and be qualified for imaging

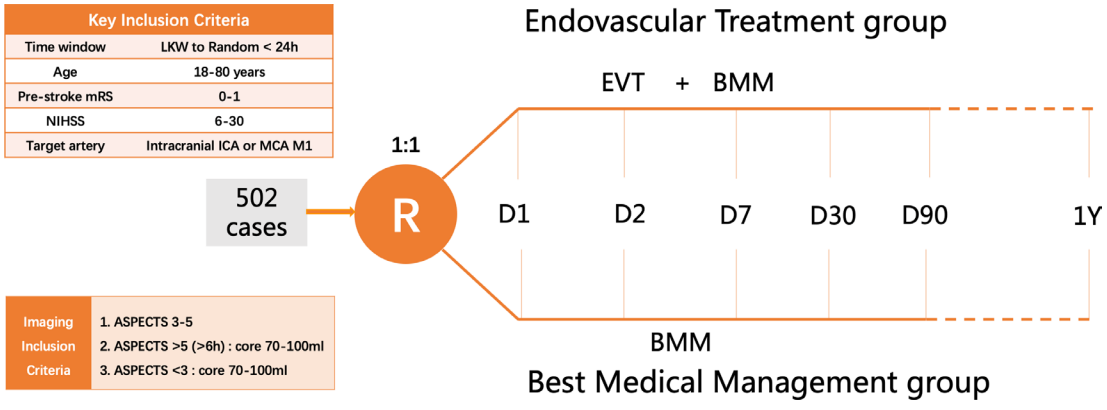

Figure 1 Study design: randomisation algorithm. ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular therapy; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MCA, middle cerebral artery.

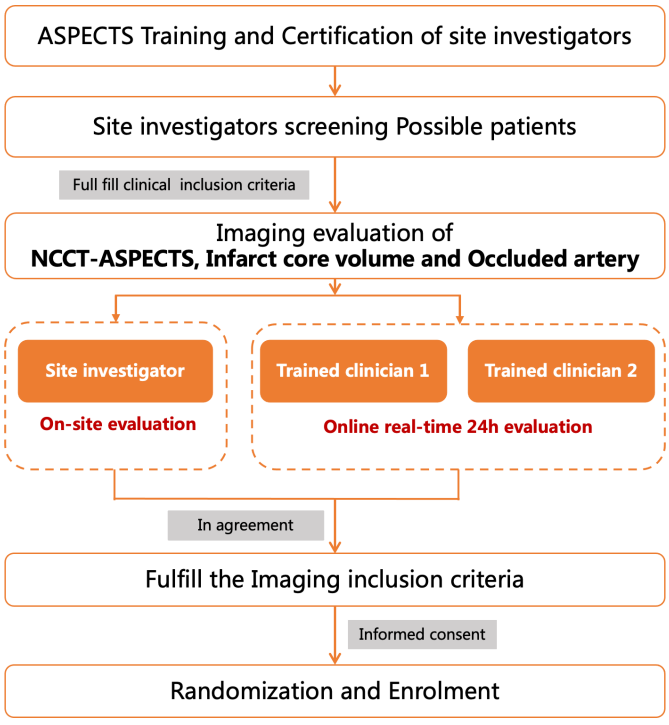

Figure 2 Imaging evaluation working flow. ASPECTS, Alberta Stroke Program Early CT Score.

assessment. During imaging screening, researchers in the subcentre 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 imaging evaluation (figure 2). The infarct core volume was automatically evaluated by iSchemaView automated RAPID software (V.5.0.4, iSchemaView, California, USA), and the infarction core volume is defined as relative cerebral blood volume (rCBF) <30% based on CTP or apparent diffusion coefficient (ADC) <620 based on MRI. Occlusion site was evaluated by CTA or MRA. Collateral status was evaluated by CTA or MRA and also by HIR in Tmax of CTP.

Primary outcomes

Ninety days (±7 days) mRS.

Secondary outcomes

1. Ninety days (±7 days) mRS 0–2.
2. Ninety days (±7 days) mRS 0–3.
3. Thirty-six 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. Thirty-six hours (±12 hours) target artery recanalisation rate assessed with CTA or MRA.

Safety outcomes

Symptomatic ICH (sICH) within 48 hours from randomisation (Heidelberg Bleeding Classification) is the primary safety endpoint of this trial.[13] Secondary safety outcomes include the following events: All-cause mortality within 90 days (±7 days); any ICH within 48 hours from randomisation (Heidelberg Bleeding Classification); decompressive hemicraniectomy during hospitalisation.

Data safety and monitoring board

The data safety and monitoring board (DSMB) will have meetings within scheduled time and monitor the progress of trial to guarantee the trial in accordance with the standards of ethics and ensure the patient safety. The DSMB is constituted by committee members of academic areas and independent statistician. All the DSMB members should not be involved in the implementation of the trial. Before the enrolment of the trial, a DSMB charter should be confirmed by all the DSMB members and executive committee members. This DSMB charter should include the membership, role and DSMB responsibilities. During the DSMB meeting, the DSMB members will generate recommendations and the DSMB chair will hand over to steering committee right away after the meeting.

Sample size

In this study, a multicentre, open, randomised, parallel control design method was used. The primary measure of efficacy was mRS score at 90±7 days after randomisation (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 analyses were planned. Adjusted level α=0.046 (two sided) and power 1−β=0.90 and (4) The sample size was allocated to the EVT 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 analyses will take place when 1/3 (168 cases) and 2/3 (336 cases) have completed a 3-month follow-up. O'Brien-Fleming boundaries will be used at the interim analysis with alpha of two-sided 0.0002 (stage 1), 0.0123 (stage 2) and 0.046 (stage 3, final analysis). PASS software (NCSS, V.11) was used to calculate the sample size.

Statistical analyses

Data will be analysed both based on intention-to-treat principle in main analysis and in per-protocol set for sensitivity analysis. T-test or Wilcoxon rank-sum test will be used for comparison between continuous variables, and χ^2 tests, Fisher's exact test or Wilcoxon sum-rank test will be used for comparison between categorical variables. For primary efficacy endpoint, an ordinal logistic regression model will be used to calculate the common OR as well as their 95% CIs. A two-sided with p<0.046 was considered significant for primary outcome. For secondary efficacy endpoints like 90-day mRS 0–2 will be analysed using a binary logistic regression model.

The infarct core volume change from baseline will be analysed by using Student's t-test or Wilcoxon rank-sum test as appropriate. χ^2 test and Fisher's exact test will be used to compare the differences in the incidence of adverse events and serious adverse events between the two groups. Ahead of the lockdown of data and the breaking of code, a final SAP will be issued. All analyses will be performed using SAS software, V.9.4 (SAS Institute) and two sided with p<0.05 will be considered significant.

Study organisation

The steering committee will have meeting twice a year to oversight the trial and give strategic input. Safety outcomes, adverse events and serious adverse events are adjusted by clinical events adjudication committee. Imaging are adjudicated by an independent imaging core lab (Tiantan Neuroimaging Center of Excellence). Trained assessors will adjudicate the effective outcomes and all the data are masked to treatment assignment. The DSMB will have meetings within scheduled time and monitor the progress of trial to guarantee the trial in accordance with the standards of ethics and ensure the patient safety. The committees are provided in online supplemental table 2.

DISCUSSION

Thrombectomy for acute large vascular occlusion patient with small infarct core is highly recommended by most guidelines. Mounting evidence indicates that thrombectomy has potential benefits for patients with low ASPECTS of 3–5 or large infarct core volumes from 70 mL to 100 mL. Currently, many randomised controlled trials are exploring the efficacy and safety of EVT for acute LVO patients with large infarct core volume.[4]

The first completed trial RESCUE-JAPAN LIMIT (NCT03702413) showed that thrombectomy is benefit in 90 days mRS 0–3 for patients with low ASPECT score.[11] However, its population was significantly biased by DWI-ASPECTS and patients with good mismatch defined by DWI/ fluid-attenuated inversion recovery (FLAIR) signal (no early FLAIR signal change) beyond 6 hours, and more than 70% of the cases were treated within 6 hours. Trials with different criteria and sample size with more cases are needed to identify the efficacy and safety of thrombectomy for LVO patients with a large infarct core based on NCCT ASPECTS or volume within the early and extended time window. Many ongoing trials are trying to address the benefit of EVT with large infarct core: Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window (TENSION; NCT03094715),[14] In Extremis Large Stroke Therapy Evaluation–ASPECT 0–5 (NCT03811769), Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (NCT03805308), A Randomized Controlled Trial to Optimize Patient's SELECT 2 (NCT03876457),[15] ANGEL-ASPECT (NCT04551664) and Stroke in patients with large Ischaemic Core: Assessment of Reperfusion therapy Impact on Outcome (SICARIO). The information of registered trials was showed in online supplemental table 3.

ANGEL-ASPECT trial is a PROBE study initiated by researchers to explore the effectiveness and safety of EVT in patients with anterior circulation LVO with ASPECTS 3–5 or infarction core volume 70–100 mL.

In this trial, we limited the range of ASPECT score and infarct core volume. We expect to decrease risks while exploring the benefits of thrombectomy for patients with large core infarction. A combination of NCCT ASPECTS and perfusion core volume when ASPECTS <3 or > 5 (6–24 hours) was used as imaging inclusion criteria. The primary imaging inclusion criteria of ANGEL-ASPECT are NCCT ASPECT score 3 to 5, and the infarct core volume 70–100 mL is used as auxiliary inclusion criteria when ASPECTS <3 or > 5 (6–24 hours). There is no unified definition of large core infarction, so this complex imaging criteria allows us to expand the potential benefit to as many patients as possible. More precisely, the imaging inclusion criteria for ANGEL-ASPECT 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 for patients with NCCT ASPECTS 3–5 is the key target population. (2) The patients with NCCT ASPECTS 0–2 and core infarction volume 70–100 mL determined by CTP or DWI MRI are also included considering the potential benefit of the volume and subjective nature of ASPECTS. 3. The patients with NCCT ASPECTS >5, between 6 and 24 hours of onset, and infarct core volume 70–100 mL, which are beyond the infarct core volume of DAWN and DEFUSE 3 criteria are also enrolled.

The benefits of expanding the time window for patients with low ASPECTS are worth expecting, so the time window of ANGEL-ASPECT is 24 hours. Subgroup analysis will focus on age, wake-up stroke, last known well to random time, NIHSS score, thrombolysis, occlusion site, ipsilateral ICA occlusion, ASPECT score, infarct volume and stroke type.

There are conflicts on definition of large infarct core[16 17] and on whether patients with ASPECTS 3–5 and CTP or ADC volume <70 mL can be considered as having large infarct core.[4] We know that if a patient has a low ASPECT score but a favourable core volume on CTP, EVT may be benefit for him.[10] This benefit has been previously evidenced by many high-quality researches[18 19] although these studies included some patients with an ASPECT score less than 6. For infarct core volume, CTP could offer a more objective measurement than ASPECT score, but this has not yet been confirmed in a high-quality trial. In our trial, we may include patients with low ASPECT score and favourable CTP-defined infarct core volume, and this allows for the comparison of these two imaging criteria. When a patient's imaging is evaluated by both ASPECT score and CTP defined infarct volume, the further subgroup analysis maybe very helpful in clarifying the mechanism if EVT is found to be benefit for large infarct core.

The goal of ANGEL-ASPECT trial is to include the maximum patients with a potential benefit large infarct

core volume for whom EVT is not recommended with level 1 evidence under current guidelines.[4] The combination imaging inclusion criteria with NCCT ASPECTS and perfusion core volume when ASPECTS <3 />5 aims to include more potential large core volume based on ASPECTS and uses perfusion as further screening to include maximal potential benefit patients.

SUMMARY AND CONCLUSIONS

ANGEL-ASPECT trial will produce objective data on whether BMM combined with EVT improves neurological outcomes for patients with large infarct core volume in acute anterior circulation LVO compared with BMM alone.

Author affiliations
[1]Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Beijing, China
[2]Department of Neurology, Beijing Tiantan Hospital, Beijing, China
[3]Clinical Research Center, Capital Medical University, Institute of Brain Disorders, Beijing, China
[4]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Beijing, China
[5]Department of Neurology, University of California, Los Angeles, California, USA
[6]Division of Neurosurgery, Department of Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[7]Department of Neurosurgery, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China

Twitter Xiaochuan Huo @Xiaochuan Huo, David S Liebeskind @dliebesk and Vitor Mendes Pereira @VitorMendesPer1

Contributors ZM, ZR and VMP designed the study; XH drafted the manuscript; YW, DSL, YW, LL, XZ, XT, DS and GM provided critical comments/revisions of the manuscript.

Funding This study was funded by Covidien Healthcare International Trading (Shanghai) Co., Ltd., Johnson & Johnson MedTech, Genesis MedTech (Shanghai) Co.,Ltd. and Shanghai HeartCare Medical Technology Co., Ltd.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The ANGEL-ASPECT trial was approved by ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2020-072-02) and all participating centres. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Xiaochuan Huo http://orcid.org/0000-0003-1264-5132
Gaoting Ma http://orcid.org/0000-0002-9374-7589
Yuesong Pan http://orcid.org/0000-0003-3082-6789
Xu Tong http://orcid.org/0000-0002-3277-6941
Dapeng Sun http://orcid.org/0000-0001-6321-5381
Liping Liu http://orcid.org/0000-0003-2943-055X
Yilong Wang http://orcid.org/0000-0002-3267-0039
David S Liebeskind http://orcid.org/0000-0002-5109-8736
Zeguang Ren http://orcid.org/0000-0002-7431-2643

REFERENCES

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:e344–418.
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;11:535–8.
3 Meyer L, Bechstein M, Bester M, *et al*. Thrombectomy in extensive stroke may not be beneficial and is associated with increased risk for hemorrhage. *Stroke* 2021;52:3109–17.
4 Ren Z, Huo X, Ma G, *et al*. Selection criteria for large core trials: rationale for the ANGEL-ASPECT study design. *J Neurointerv Surg* 2022;14:107–10.
5 Román 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;17:895–904.
6 Campbell BCV, Majoie CBLM, 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;18:46–55.
7 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;76:1147–56.
8 Seners P, Oppenheim C, Turc G, *et al*. Perfusion imaging and clinical outcome in acute ischemic stroke with large core. *Ann Neurol* 2021;90:417–27.
9 Kerleroux B, Janot K, Hak JF, *et al*. Mechanical thrombectomy in patients with a large ischemic volume at presentation: systematic review and meta-analysis. *J Stroke* 2021;23:358–66.
10 Bouslama M, Barreira CM, Haussen DC, *et al*. Endovascular reperfusion outcomes in patients with a stroke and low aspects is highly dependent on baseline infarct volumes. *J Neurointerv Surg* 2022;14:117–21.
11 Yoshimura S, Sakai N, Yamagami H, *et al*. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med* 2022;386:1303–13.
12 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;5:159–76.
13 von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
14 Bendszus M, Bonekamp S, Berge E, *et al*. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke* 2019;14:87–93.
15 Sarraj A, Hassan AE, Abraham M, *et al*. A randomized controlled trial to optimize patient's selection for endovascular treatment in acute ischemic stroke (SELECT2): study protocol. *Int J Stroke* 2022;17:689–93.
16 Jadhav AP, Hacke W, Dippel DWJ, *et al*. Select wisely: the ethical challenge of defining large core with perfusion in the early time window. *J Neurointerv Surg* 2021;13:497–9.
17 Sarraj A, Campbell B, Ribo M, *et al*. Selection criteria for large core trials: dogma or data? *J Neurointerv Surg* 2021;13:500–4.
18 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;378:708–18.
19 Campbell BCV, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009–18.

Supplemental tables

Supplemental table 1. Participation centers

Department	Hospital	City	Province	Site PI
Department of Interventional Neuroradiology	Beijing Tiantan Hospital, Capital Medical University	Beijing	Beijing	Zhongrong Miao
Department of Emergency	Xiangtan Central Hospital	Xiangtan	Hunan	Guangxiong Yuan
Department of Neurology	Linyi People's Hospital	Linyi	Shandong	Hongxing Han
Department of Neurology	Zhangzhou Affiliated Hospital of Fujian Medical University	Zhangzhou	Fujian	Wenhuo Chen
Department of Neurosurgery	Tianjin huanhu hospital	Tianjin	Tianjin	Ming Wei
Department of Neurology	Anyang People's Hospital	Anyang	Henan	Jiangang Zhang
Department of Neurology	Yijishan Hospital of Wannan Medical College	Wuhu	Anhui	Zhiming Zhou
Department of Neurology	The first people's hospital of Chenzhou	Chenzhou	Hunan	Xiaoxi Yao
Department of Neurology	Bin zhou People's Hospital	Binzhou	Shandong	Guoqing Wang
Department of Neurology	Yancheng Third People's Hospital	Yancheng	Jiangsu	Weigen Song
Department of Neurology	Lishui Municipal Central Hospital	Lishui	Zhejiang	Xueli Cai
Department of Neurology	China-Japan Union Hospital of Jilin University	Changchun	Jinlin	Guangxian Nan
Department of Neurointervention	Dalian Municipal Central Hospital affiliated with Dalian Medical University	Dalian	Liaoning	Di Li
Department of Neurosurgery	Guangdong Provincial Hospital of Chinese Medicine	Guangzhou	Guangdong	Alvin Yi-Chou Wang
Department of Neurology	ZhongShan City People's Hospital	Guangzhou	Guangdong	Wentong Ling
Department of Neurology	Shantou Central Hospital	Shantou	Guangdong	Chuwei Cai
Department of Neurology	Nanyang Central Hospital	Nanyang	Henan	Changming Wen
Department of Neurology	Taizhou hospital of Zhejiang Province	Taizhou	Zhejiang	En Wang
Department of Neurosurgery	Liaocheng People's Hospital	Liaocheng	Shandong	Liyong Zhang
Department of Neurology	Baotou Centre Hospital	Baotou	Inner Mongolia	Changchun Jiang
Department of Neurology	Shenzhen Hospital, Southern Medical University	Shenzhen	Guangdong	Yajie Liu
Department of Neurology	Maoming People's Hospital	Maoming	Guangdong	Geng Liao
Department of Neurology	The Second Affiliated Hospital of GuangZhou Medical University	Guangzhou	Guangdong	Xiaohui Chen

Department of Cerebrovascular Disease	Henan Provincial People's Hospital, Zhengzhou University	Zhengzhou	Henan	Tianxiao Li
Department of Neurology	Yongchuan Hospital of Chongqing Medical University	Chongqing	Chongqing	Shudong Liu
Department of Neurology	The affiliated hospital of South West medical university	Luzhou	Sichuan	Jinglun Li
Department of Neurology	Shanxi Provincial People's Hospital	Taiyuan	Shanxi	Yaxuan Sun
Department of Neurology	The Second Affiliated Hospital to Xiamen Medical College	Xiamen	Fujian	Na Xu
Department of Neurology	Shengli Oilfield Central Hospital	Dongying	Shandong	Zong'en Gao
Department of Neurology	Songyuan Jilin oil Field Hospital	Songyuan	Jilin	Dongsheng Ju
Department of Interventional Neuroradiology	Liao Cheng the third people's hospital	Liaocheng	Shandong	Cunfeng Song
Department of Neurology	The First People's Hospital of Changzhou	Changzhou	Jiangsu	Jinggang Xuan
Department of Neurology	Taiyuan Central Hospital	Taiyuan	Shanxi	Feng Zhou
Department of Neurology	Affiliated Jiangmen Traditional Chinese Medicine Hospital of Ji'nan University	Jiangmen	Guangdong	Qing Shi
Department of Neurology	Sichuan Mianyang 404 Hospital	Mianyang	Sichuan	Jun Luo
Department of Neurology	JingJiang People's Hospital, the Seventh Affiliated Hospital of Yangzhou University	Jingjiang	Jiangsu	Yan Liu
Department of Neurosurgery	Tianjin TEDA Hospital	Tianjin	Tianjin	Zaiyu Guo
Department of Neurosurgery	The second Nanning People's Hospital	Nanning	Guangxi	Tong Li
Department of Neurology	West China Hospital, Sichuan University	Chengdu	Sichuan	Hongbo Zheng
Department of Neurosurgery	First Affiliated Hospital School of Medicine Shihezi University	Shihezi	Xinjiang	Linzhi Dai
Department of Neurology	Siping Central People's Hospital	Siping	Jilin	Junfeng Zhao
Emergency and Critical Stroke Ambulance Center	Langfang Changzheng Hospital	Langfang	Hebei	Liqiang Gui
Department of Neurology	Beijing Luhe Hospital, Capital Medical University	Beijing	Beijing	Xiaokun Geng
Department of Neurology	Mianyang Central Hospital	Mianyang	Sichuan	Yufeng Tang
Department of Neurology	Hangzhou First People's Hospital	Hangzhou	Zhejiang	Congguo Yin
Department of Neurosurgery	The affiliated Hospital of Guizhou Medical University	Guiyang	Guizhou	Hua Yang

Supplemental table 2. Study organization

Member	Department	Hospital
Steering Committee		
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
Independent imaging Core Lab		
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
Data safety and monitoring board		
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		
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
Executive committee		
Zhongrong Miao	Department of Interventional Neuroradiology	Beijing Tiantan Hospital, Capital Medical University

Xiaochuan Huo	Department of Interventional Neuroradiology	Beijing Tiantan Hospital, Capital Medical University
Gaoting Ma	Department of Interventional Neuroradiology	Beijing Tiantan Hospital, Capital Medical University
Guangxiong Yuan	Department of Emergency	Xiangtan Central Hospital
Hongxing Han	Department of Neurology	Linyi People's Hospital
Wenhuo Chen	Department of Neurology	Zhangzhou Affiliated Hospital of Fujian Medical University
Ming Wei	Department of Neurosurgery	Tianjin huanhu hospital
Jiangang Zhang	Department of Neurology	Anyang People's Hospital
Zhiming Zhou	Department of Neurology	Yijishan Hospital of Wannan Medical College
Xiaoxi Yao	Department of Neurology	Chenzhou First One Hospital
Guoqing Wang	Department of Neurology	Bin zhou People's Hospital
Weigen Song	Department of Neurology	Yancheng Third People's Hospital
Xueli Cai	Department of Neurology	Lishui Municipal Central Hospital
Guangxian Nan	Department of Neurology	China-Japan Union Hospital of Jilin University
Di Li	Department of Neurointervention	Dalian Municipal Central Hospital affiliated with Dalian Medical University
Yizhou Wang	Department of Neurosurgery	Guangdong Provincial Hospital of Chinese Medicine
Wentong Ling	Department of Neurology	ZhongShan City People's Hospital
Chuwei Cai	Department of Neurology	Shantou Central Hospital
Changming Wen	Department of Neurology	Nanyang Central Hospital
En Wang	Department of Neurology	Taizhou hospital of Zhejiang Province
Liyong Zhang	Department of Neurosurgery	Liaocheng People's Hospital
Changchun Jiang	Department of Neurology	Baotou Centre Hospital
Yajie Liu	Department of Neurology	Shenzhen Hospital, Southern Medical University
Geng Liao	Department of Neurology	Maoming People's Hospital
Xiaohui Chen	Department of Neurology	The Second Affiliated Hospital of GuangZhou Medical University
Tianxiao Li	Department of Cerebrovascular Disease	Henan Provincial People's Hospital, Zhengzhou University
Shudong Liu	Department of Neurology	Yongchuan Hospital of Chongqing Medical University
Jinglun Li	Department of Neurology	The affiliated hospital of South West medical

		university
Yaxuan Sun	Department of Neurology	Shanxi Provincial People's Hospital
Na Xu	Department of Neurology	The Second Affiliated Hospital to Xiamen Medical College
Zong'en Gao	Department of Neurology	Shengli Oilfield Central Hospital
Dongsheng Ju	Department of Neurology	Songyuan Jilin oil Field Hospital
Cunfeng Song	Department of Interventional Neuroradiology	Liao Cheng the third people's hospital
Jinggang Xuan	Department of Neurology	The First People's Hospital of Changzhou
Feng Zhou	Department of Neurology	Taiyuan Central Hospital
Qing Shi	Department of Neurology	Affiliated Jiangmen Traditional Chinese Medicine Hospital of Ji'nan University
Jun Luo	Department of Neurology	Sichuan Mianyang 404 Hospital
Yan Liu	Department of Neurology	JingJiang People's Hospital, the Seventh Affiliated Hospital of Yangzhou University
Zaiyu Guo	Department of Neurosurgery	Tianjin TEDA Hospital
Tong Li	Department of Neurosurgery	The second Nanning People's Hospital
Hongbo Zheng	Department of Neurology	West China Hospital, Sichuan University
Linzhi Dai	Department of Neurosurgery	First Affiliated Hospital School of Medicine Shihezi University
Junfeng Zhao	Department of Neurology	Siping Central People's Hospital
Liqiang Gui	Emergency and Critical Stroke Ambulance Center	Langfang Changzheng Hospital
Xiaokun Geng	Department of Neurology	Beijing Luhe Hospital, Capital Medical University
Yufeng Tang	Department of Neurology	Mianyang Central Hospital
Congguo Yin	Department of Neurology	Hangzhou First People's Hospital
Hua Yang	Department of Neurology	The affiliated Hospital of Guizhou Medical University

Supplemental table 3. Registered Large infarct core volume thrombectomy trials

Trial	TENSION	LASTE	TESLA	RESCUE - Japan LIMIT	SELECT - 2	ANGEL - ASPECT
NCT number	NCT03094715	NCT03811769	NCT03805308	NCT03702413	NCT03876457	NCT04551664
Participating Country(ies)	Europe, Canada	Europe, United States	United States	Japan	United States, Canada, Europe	China
Major imaging inclusion criteria	NCCT or DWI ASPECTS 3 - 5	NCCT or DWI ASPECTS 0 - 5 (4–5 for > 80 y)	NCCT or ASPECTS 2 - 5	CT ASPECTS 3 - 5 or DWI ASPECTS 3 - 5	1. ASPECTS ≥6 and CTP core ≥50 cc 2. ASPECTS 3 - 5 and core ≥50 cc 3. ASPECTS 3 - 5 and core <50 cc	1. ASPECTS 3 - 5 2. ASPECTS >5 (>6 h) and core 70 - 100 cc 3. ASPECTS <3 and core 70 - 100 cc

Trial	TENSION	LASTE	TESLA	RESCUE - Japan LIMIT	SELECT - 2	ANGEL - ASPECT
NIHSS score	<26	>5	>6	≥6	≥6	6 - 30
Age, y	>18	≥18	18 - 85	>18	18 - 85	18 - 80
Time window	<12 h LSW	<6.5 h LKW	Random <24 h	Random <6 h LKW, 6 - 24 FLAIR (-)	Treat <24 h (0 - 12 vs 6 - 24)	Random <24 h
Occlusion site	Terminal ICA and MCA M1	Intracranial ICA, MCA M1 or M1 - M2	Terminal ICA and M1	Terminal ICA and M1	ICA or MCA M1, tandem	Terminal ICA and/or MCA M1 Tandem occlusion included
Required time limit from randomization to puncture	No	Yes Randomization to arterial access 30 min	No	Yes Randomization to arterial access 60 min	No	Yes Randomization to arterial access 60 min
Bridging therapy permitted	Yes	Yes	Yes	Yes	Yes	Yes
Intervention model	EVT, no specified device	EVT, no specified device	FDA - approved EVT devices	EVT, no specified device	EVT with SR Device: Trevo, Solitaire, and EmboTrap	EVT, IA - thrombolysis, angioplasty Device: Solitaire, EMBOTRAP, Reco SR, Penumbra aspiration catheter, or CFDA - approved EVT devices
Major exclusion criteria	Mass effect on CT Vascular disease prevent MT (eg, aortic dissection or aneurysm, no arterial transfemoral access)	Suspicion of aortic dissection, excessive tortuosity of cervical vessels on vascular imaging Multiple occlusion Cervical tandem lesion that requires stent placement	Refractory hypertension Mass effect on CT Tandem lesion Difficult endovascular access on vascular images	Mass effect on CT Clinical evidence of chronic occlusion High risk of hemorrhage (platelet <40,000/μL, APTT >50 s or PT - INR >3.0)	Mass effect on CT Inability to undergo CTA and/or CTP tPA 3 - 4.5 h With special situation* ICA dissection or aortic dissection Multiple occlusions	Refractory hypertension Mass effect on CT Multiple occlusions INR >1.7 or APTT >35 s; platelet count $<100\times10^9$/L
Primary outcome	mRS score shift analysis	mRS score at 90 and 180 d	Utility - weighted 90 - d mRS score	mRS score 0 - 3 at 90 d	Shift on 90 - d mRS score	mRS score at 90 d
Actual study start date	July 20, 2018	April 7, 2019	July 16, 2019	November 2018	October 11, 2019	September 28, 2020

Source: https://clinicaltrials.gov. ANGEL-ASPECT, Study of EVT in Acute Anterior Circulation LVO Patients with a largE infarCT core; Core: rCBF <30% on CT perfusion or ADC <620. ADC indicates apparent diffusion coefficient; APTT, activated partial thromboplastin time; ASPECTS, Alberta Stroke Program Early CT Score; CFDA, China Food and Drug Administration; CT, computed tomography; CTA, computed tomography angiography; CTP, computed tomography perfusion; DWI, diffusion-weighted imaging; EVT, endovascular treatment; FDA, US Food and Drug Administration; FLAIR, fluid-attenuated inversion recovery; IA, intra-arterial; ICA, internal carotid artery; INR, international normalized ratio; LASTE, Large Stroke Therapy Evaluation; LKW, last known well; LSW, last seen well; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NCCT, noncontrast CT; NCT, National Clinical Trial; NIHSS, National Institutes of Health Stroke Scale; PT-INR, Pro-thrombin Time-International Normalized Ratio; RESCU-Japan LIMIT, Randomized Controlled Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core; rCBF, relative cerebral blood flow;SELECT-2, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; SR, stent retriever; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke and tPA, tissue plasminogen activator.

*(1) Age >80 y, (2) current anticoagulant use, (3) history of diabetes and prior stroke, (4) NIHSS >25, and (5) ischemic involvement of more than one-third of MCA territory.