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Association between stroke subtypes and outcomes of endovascular therapy: a post-hoc analysis of the ANGEL-ASPECT Trial

Da Lu,[1] Raynald ,[2] Dapeng Sun ,[2] Na Zheng,[3] Bohao Zhang ,[1] Leilei Luo ,[1] Sifei Wang,[1] Sihu Pan,[1] Yuchao Dou ,[1] Mengxing Wang ,[4] Yuesong Pan,[4] Xiaochuan Huo ,[2] Zhongrong Miao,[2] Ming Wei[5]

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DL and R contributed equally.

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[1]Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin, China
[2]Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Beijing, China
[3]Department of Traditional Chinese Medicine, Tianjin Huanhu Hospital, Tianjin, China
[4]Beijing Tiantan Hospital, Beijing, China
[5]Tianjin Huanhu Hospital, Tianjin, China

Correspondence to
Dr Ming Wei;
drweiming@163.com

ABSTRACT

Objectives Our study aims to examine the value of endovascular therapy (EVT) and its comparison to medical management (MM) in ischaemic stroke patients accompanied by large artery atherosclerosis (LAA) and non-LAA

Methods modified Rankin scale score (mRS) was evaluated at 90 days post the stroke attack and was considered as the primary outcome. Other outcomes measured in this study included score changes of 0–2 and 0–3 on the mRS. The occurrence of symptomatic intracranial haemorrhage at 24 hours after EVT was also measured as a safety endpoint. Logistic regression analysis was used to determine the associations.

Results In the LAA group, no significant difference in mRS at 90-day (median IQR 3 (2–5) vs 4 (3–4), 95% CI 0.53 to 2.00, p=0.924), mRS 0–2 and mRS 0–3 was observed between EVT and MM groups. However, in the non-LAA group, patients who underwent EVT had lower 90-day mRS scores (4 (2–5) vs 4 (3–5), generalised OR 1.47, 95% CI 1.14 to 1.88, p<0.001). No interaction effect on the primary outcomes between treatment options and aetiology. More intracranial haemorrhage events within 48 hours were identified in the EVT group for both LAA and non-LAA cohorts (LAA: 40.98% vs 9.62%, relative risk (RR) 4.26, 95% CI 1.76 to 10.34, p<0.001; non-LAA, 52.07% vs 19.65%, RR 2.65, 95% CI 1.90 to 3.70, respectively).

Conclusions For large infarcts, EVT may be more effective than MM for patients with non-LAA aetiology, but not for those with LAA stroke. As no interaction effect was found, the benefit of EVT compared with MM did not vary by stroke subtypes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The effectiveness and safety of endovascular therapy (EVT) has been gradually recognised worldwide. However, its value in patients with large lesions has not been well examined, especially for patients with aetiologies.

WHAT THIS STUDY ADDS

⇒ For individuals with a non-LAA (non-large artery atherosclerosis) cause, EVT has shown better efficacy results compared with medical management. However, this advantage may not extend to large infarct patients with LAA stroke.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For large ischaemic strokes, a precise and selective approach is advisable for individuals experiencing LAA-related strokes when contemplating the use of EVT as a treatment method.

INTRODUCTION

Endovascular treatment (EVT) has become the conventional approach for treating acute ischaemic stroke (AIS) patients who have large-vessel occlusion (LVO). The growing body of literature on the role of EVT in AIS with LVO has provided valuable insights worldwide.[1 2] However, it is well established that the distribution of stroke aetiologies varies among different ethnicities and countries, particularly between Western and Asian populations.[3 4] The value of EVT in patients with different stroke aetiologies remains uncertain.[5 6] Nevertheless, recent prospective registry studies have indicated similar functional outcomes across various stroke subtypes.[7 8] Furthermore, recent researches have demonstrated superior outcomes with EVT administered within 24 hours compared with medical management (MM) alone for large infarct with LVO,[9 10] supporting its clinic use in these patients. Nonetheless, it has been acknowledged that EVT is associated with a higher incidence of intracranial haemorrhages, which may impede its clinical applications.[11]

Therefore, a multicentre study is necessary to validate the efficacy and safety of EVT in AIS patients with different stroke aetiologies. In this subgroup analysis, we aim to compare the efficacy and safety of EVT versus MM in AIS patients with LVO caused by different stroke aetiologies according to the TOAST

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(The Trial of ORG 10172 in Acute Stroke Treatment classification) subtypes.

METHODS

Patient population

This open-label study was carried out at 46 stroke centres across China with blinded end-point evaluation. Patients were either referred from centres lacking endovascular treatment capabilities or initially examined at one of the trial centres. Before enrolling, all patients or their authorised representatives gave written informed consent. The authors take responsibility for the accuracy, comprehensiveness and adherence of the trial data to the established protocol.

Detailed inclusion/exclusion criteria were described before.[10] The large infarct was defined as any of the following criteria: Alberta Stroke Programme Early CT Score (ASPECTS) of 3–5 on CT scan within 24 hours from disease onset, regardless of infarction volume; ASPECTS of 0–2 with an infarction volume between 70 and 100 mL within 24 hours from disease onset; or ASPECTS higher than 5 on CT from 6 to 24 hours from disease onset and infarction volume between 70 and 100 mL.

Baseline data collection

Patients' parameters including demographics, the ASPECTS from initial CT examination, the location of occlusions, presence of tandem occlusions, infarction core volume, utilisation of thrombolysis, the occurrence of wake-up stroke, time-related metrics (such as onset to door, onset to imaging, onset to randomisation and onset to recanalisation), preoperative blood flow, immediate and final extend Thrombolysis in Cerebral Infarction (eTICI) scores, achievement of target recanalisation at 36 hours, postoperative National Institute of Stroke Scale (NIHSS) scores were collected. Moreover, the modified Rankin scale (mRS) scores measured at 90 days were collected from patients via telephone interviews. Data including preoperative and postoperative imaging and assessment results were transmitted to the central lab for further evaluation.

Stroke subtype definition

Strokes were classified into two categories, namely large artery atherosclerosis (LAA) and non-LAA subtypes. This subtype was determined by both imaging and angiographic observations. Specifically, the diagnosis was first made based on reconstructed images derived from CT angiography (CTA) or MR angiography (MRA) before operation and further defined by digital subtraction angiography during the operation. LAA was defined as having significant narrowing (≥50%) or blockage of the artery affected by atherosclerosis that was observed during EVT. Symptoms such as leg pain, transient ischaemic episodes in the same area or the presence of carotid bruit or weak pulses were also used to confirm the diagnosis.

Outcomes

The primary outcome measure of this study was to assess and compare patients' modified Rankin score at 90 days postoperation between two treatments, aiming to provide reference for clinical application. The primary endpoint was to measure the change of mRS at 90 days. Secondary outcomes encompassed early neurological improvement, defined as an NIHSS score of 0–1 or an improvement in NIHSS score of at least 10 points at 36 hours postrandomisation, changes of infarction volume from baseline to 7 days after receiving treatment or at hospital discharge (whichever occurred earlier) if using CT or to 3 days after receiving treatment if using MRI for imaging, and recanalisation rate of the involved artery at 36 hours which was determined by CTA or MRA.

Safety outcomes included symptomatic intracranial haemorrhage within 48 hours after randomisation, defined by the Heidelberg bleeding classification (a rise of at least 4 points in the NIHSS score or a rise of at least 2 points of NIHSS subcategory with any intracranial bleeding on imaging). Furthermore, any intracranial haemorrhage occurring within 48 hours, death within 90 days following stroke onset, and the necessity for decompressive craniectomy during hospitalisation were also measured and considered as safety outcomes. Assessment of the mRS score at 90 days was conducted through telephone interviews, with recordings made for quality control purposes. All adverse events were verified by a clinical-event adjudication committee, composed of members who were unaware of the assignments of trial groups.

Imaging assessments

Throughout the study, imaging assessments were conducted on specific time points including baseline, 36 hours (±12 hours) and 7 days (±1 day) after receiving the treatments. The results were sent to an independent and blinded imaging core laboratory for evaluation. Various parameters, including the baseline ASPECTS value, arterial occlusion site, reperfusion and follow-up intracranial haemorrhage, were assessed. Infarction volumes were measured using the RAPID software V.5.0.4 (iSchemaView) based on diffusion-weighted imaging at both baseline and follow-up. The evaluation was conducted simultaneously by site clinicians and coordinators in the central lab in real time via the online platform. The RAPID system used CT perfusion (CTP) imaging or MRI to measure the infarction volume, which was designed as the area with very low blood flow or diffusion. In the endovascular therapy group, reperfusion was measured by the eTICI scale, showing at least moderate reperfusion. At 36 hours, follow-up CTA or MRA evaluated successful recanalisation, defined by a modified arterial occlusive lesion grade of 2 or 3.

Statistical analysis

Data were presented as proportions for categorical variables while median and IQR were for continuous variables.

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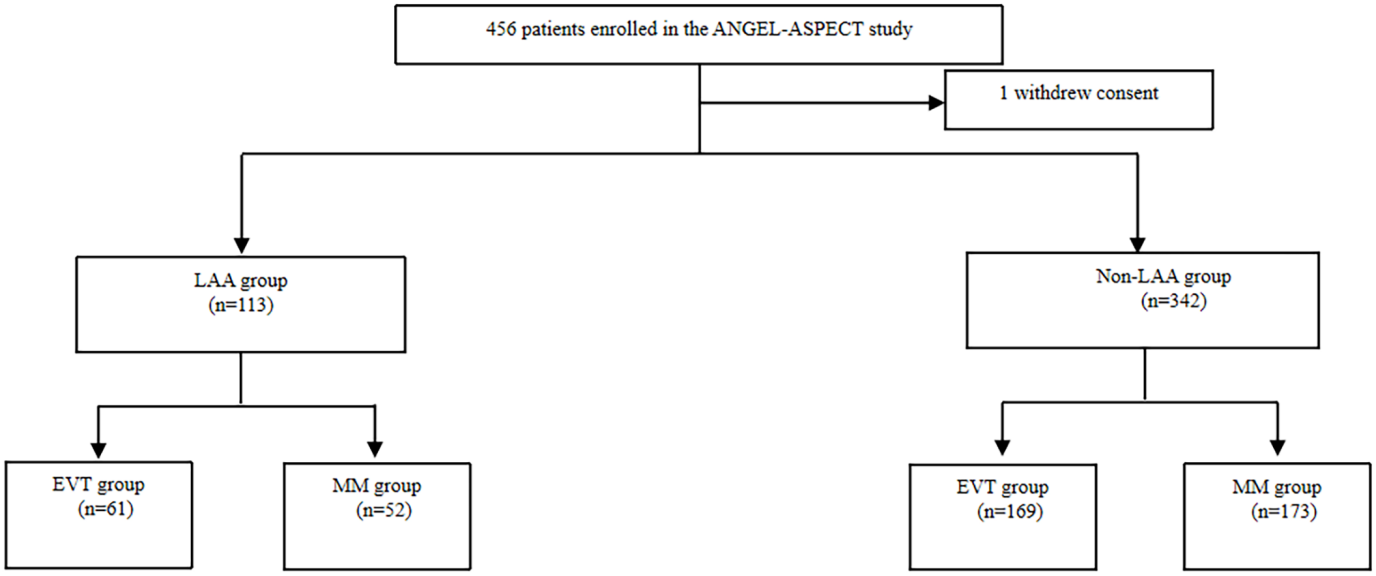

Figure 1 Flow chart of patient selection. EVT, endovascular treatment; LAA, large artery atherosclerotic; MM, medical management; ANGEL-ASPECTS, Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core.

We divided patients into LAA groups and non-LAA groups. To compare baseline characteristics between patients undergoing EVT and MM in each group, we employed the Pearson χ^2 test for analysis or Wilcoxon rank sum test as indicated. We used a Wilcoxon-Mann-Whitney method to estimate the generalised OR (gOR) and 95% CI for the ordinal shift in mRS score towards a better outcome, which was the primary outcome. The Cox proportional-hazards model was adopted to estimate the HR with 95% CI for death within 90 days, generalised linear model to calculate mean differences with 95% CI for change from baseline in infarct-core volume, and Cochran-Mantel-Haenszel method was adopted to determine relative risk (RR) with 95% CI for other study outcomes. We also explore the interaction effect between LAA and treatment options on all the study outcomes by Cochran-Mantel-Haenszel method, generalised linear or Cox regression models. Variables with a $p<0.05$ in the univariable analysis were regarded as possible predictors. A significance level of $\alpha=0.05$ (two sided) was set for all analyses. SAS software was applied for all statistical analyses (V.9.4).

RESULTS

Baseline characteristics

As shown in figure 1, 1 of the 456 patients in the ANGEL-ASPECTS (Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core) was excluded due to withdrawn consent. Of the remaining 455 patients, 113 were LAA and 342 were non-LAA. No significant difference in baseline characteristics was observed between the EVT and MM groups (all $p>0.05$). In the LAA group, patients with EVT were 67 (58–70) years old, median NIHSS were 15 (13–19) and 77.05% were male sex, 40.98% were ICA occlusion and 59.02% were M1 occlusion and 22.95% were undergoing IVT; patients with MM were 67 (57–72) years old, median NIHSS were 15 (13–18) and 80.77% were male sex, 34.62% were ICA occlusion and 65.38% were M1 occlusion, and 32.69% were undergoing IVT. In the non-LAA group, patients with EVT were 69 (62–74) years old, median NIHSS were 16 (13–20) and 52.07% were male sex, 34.32% were ICA occlusion, 64.5% were M1 occlusion, 1.18% were M2 occlusion and 30.77% were undergoing IVT; patients with MM were 68 (61–73) years old, median NIHSS were 15 (12–19) and 58.96% were male sex, 36.42% were ICA occlusion, 62.43% were M1 occlusion, 1.16% were M2 occlusion and 26.59% were undergoing IVT. Additionally, the rate of successful recanalisation was higher among patients in the non-LAA group compared with those in the LAA group (83% vs 75.4%) (online supplemental table 1).

Outcomes

The results for different stroke aetiologies based on various treatment modalities are presented in online supplemental table 2. In the LAA group, 90-day mRS (median (IQR), 3 (2–5) vs 4 (3–4), gOR 1.03, 95% CI 0.53 to 2.00, p=0.924), mRS 0–2 (27.87% vs 15.38%, RR 1.81, 95% CI 0.73 to 1.51, p=0.795) and mRS 0–3 (52.46% vs 50.00%, RR 1.05, 95% CI 0.73 to 1.51, p=0.795) were not different between EVT and MM groups. In the non-LAA population, the distribution of 90-day mRS scores after stroke was lower in the EVT group (4 (2–5) vs 4 (3–5), gOR 1.47, 95% CI 1.14 to 1.88, p<0.001). Additionally, the EVT group showed a higher proportion of patients with mRS scores of 0–2 (30.77% vs 10.40%, 2.96, 95% CI 1.81 to 4.84, p<0.001) and 0–3 (44.97% vs 28.32%, RR 1.59, 95% CI 1.19 to 2.12, p=0.001) at 90 days. Furthermore, there were higher rates of target artery recanalisation at

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36 hours in the EVT group for both the LAA (73.68% vs 53.19%, RR 1.39: 95% CI 1.02 to 1.89, p=0.031) and non-LAA populations (90.71% vs 30.66%, RR 2.96: 95% CI 2.29 to 3.82, p<0.01). Among the non-LAA population, a higher proportion of patients in the EVT group underwent decompressive craniectomy during hospitalisation (8.88% vs 3.47%, RR 2.56, 95% CI 1.01 to 6.44, p=0.038). The incidence of any intracranial haemorrhage within 48 hours was significantly higher in the EVT group for both the LAA (40.98% vs 9.62%, RR 4.26, 95% CI 1.76 to 10.34, p<0.001) and non-LAA populations (52.07% vs 19.65%, RR 2.65, 95% CI 1.90 to 3.70 p<0.001). Further analysis revealed significant interactions between EVT and changes in infarct volume (p=0.014) and target artery recanalisation rates at 36 hours (p<0.001).

DISCUSSION

The major finding of the current study was that in large infarct setting, in large infarct patients with non-LAA aetiological type, EVT could lead to better clinical outcomes than MM but not in large infarct patients with LAA stroke, indicating that in large ischaemic stroke, patient with non-LAA aetiological stroke should be highly selective for EVT.

The relatively diminished benefit observed in the LAA group following endovascular treatment (EVT) can potentially be attributed to the longer procedure duration, which signifies increased procedural complexity and a longer monitoring period required to ensure the absence of reocclusion following angioplasty or stent deployment.[5] In AIS patients who have LVO, time is of critical importance, and in the context of large ischaemic stroke, there is a greater need for expedited reperfusion to salvage viable brain tissue. A recent meta-analysis of endovascular trials highlighted the significance of time intervals within the hospital setting over the period preceding hospital arrival. Considering the fact that procedure time is such a substantial factor for prognosis,[12] the extended procedure duration observed in the LAA group may have contributed to comparable functional outcomes with those who underwent MM. In the present study, the procedural workflow for patients with LAA mirrored that of those non-LAA. However, individuals with LAA who underwent EVT tended to exhibit prolonged onset-to-door (439 min vs 323 min) or onset-to-imaging (537 min vs 377 min) intervals compared with counterparts in the non-LAA group. A plausible rationale for this observation could be attributed to patients with intracranial atherosclerosis-LVO, who often manifest with comparatively milder symptoms owing to a more robust collateral circulation. Consequently, these patients may undergo a more conservative approach initially, with closer observation of fluctuating symptoms rather than an immediate recourse to aggressive therapeutic interventions.

Another plausible explanation for the discrepancy could be the lesser change in infarct core volume among patients who underwent EVT in the non-LAA population compared with those in the LAA cohort. The assessment of ischaemic core volume on baseline non-contrast CT, CTP or diffusion-weighted MRI has gained widespread acceptance as a selection criterion and a critical factor in determining acute stroke treatment decisions, both in the early and late time windows (beyond 6 hours after the last known well).[13] There exists a moderate correlation between infarct volume and functional outcomes, as the variability in tissue vulnerability contributes to heterogeneity within the ischaemic tissue. Specifically, even if the tissue appears infarcted on imaging, it is possible that it may still possess some salvageable elements and exhibit recovery over time.[14] Our data showed a trend similar to another study that found that patients with smaller tissue damage were associated with better prognosis. Although the differences were not statistically significant in our study, the consistency of our results with previous investigations suggests the potential influence of infarct volume on treatment outcomes and warrants further exploration and validation in future research. These findings further underscore the pivotal role of infarct volume as a biomarker following intra-arterial stroke therapy.[15]

Another important finding from our study is the observation that within the non-LAA population, a greater proportion of patients in the EVT group underwent decompressive craniectomy during hospitalisation. Patients with LAA stroke often have a more robust collateral circulation. The investigation of cerebral collateral circulation has emerged as a crucial aspect in stratifying patients who had a stroke, with numerous studies indicating improved outcomes among those with well-developed collaterals. Strong collateral circulation is believed to play a role in decelerating the progression of core infarction. Conversely, inadequate collateral circulation tends to result in larger infarct volumes during the early stages of stroke evolution, thereby potentially necessitating decompressive hemicraniectomy despite successful revascularisation in the EVT cohort.

Our study is subject to several limitations that should be acknowledged. First, our findings may not apply to other populations since we only included Chinese patients. Second, potential confounding factors such as collateral circulation status and thrombus characteristics were not analysed, which may play a significant role in determining outcomes across different subtypes of stroke. The absence of these analyses may limit the comprehensive understanding of the underlying mechanisms and potential treatment effects. Third, the study did not incorporate specific imaging parameters that could provide valuable insights into the characteristics of different stroke aetiologies. The inclusion of such imaging assessments would have enhanced the accuracy and depth of our analysis. Despite these limitations, it is important to note that the selection bias and reliability of our findings were well controlled due to the randomised design and the involvement of a relatively large population across different sites.

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CONCLUSIONS

Our study showed that no significant difference was observed among patients who had a stroke with large infarction who received either EVT or MM treatment across various stroke aetiologies. However, patients with non-LAA aetiology displayed a tendency to derive greater benefit from EVT compared with MM. These results underscore the importance of tailored treatment for patients with different aetiologies.

Contributors ZM and MWei planned the study; DL, R and DS analysed the data, interpreted the findings and wrote the manuscript; NZ, LL, SW, SP, YD, MWang and SW contributed to data collection; YP and XH provided critical comments/revisions of the manuscript. ZM and MW are responsible for the overall content. ZM and MW are the guarantor for this work and accepts responsibility for the data presented.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and the ANGEL-ASPECT trial was approved by the 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 Data are available on reasonable request.

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ORCID iDs

Raynald http://orcid.org/0000-0002-4749-3514
Dapeng Sun http://orcid.org/0000-0001-6321-5381
Bohao Zhang http://orcid.org/0000-0002-6524-4028
Leilei Luo http://orcid.org/0000-0003-4843-5225
Yuchao Dou http://orcid.org/0000-0002-2834-8805
Mengxing Wang http://orcid.org/0000-0002-4245-4014
Xiaochuan Huo http://orcid.org/0000-0003-1264-5132

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