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Effectiveness and safety of bridging therapy and endovascular therapy in patients with large cerebral infarctions: from ANGEL-ASPECT

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ABSTRACT

Background and purpose The benefits of thrombolytic therapy before endovascular thrombectomy in cases of acute ischaemic stroke, with a large infarction volume, remain unclear. This analysis aims to evaluate the effectiveness and safety of bridging therapy and endovascular therapy among patients with large cerebral infarctions.

Methods In this post-hoc analysis of the multicentre prospective study of ANGEL-ASPECT (Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core), participants were divided into two groups: an endovascular therapy group and a bridging therapy group. The primary outcome was the modified Rankin Scale (mRS) score at 90 days. The primary safety outcome was symptomatic intracranial haemorrhage. Ordinal logistic regression was performed to compare the primary endpoint between the two groups. Subgroup analyses were conducted to further explore potential risk factors associated with the outcomes.

Results 122 patients were included, of whom 77 (63%) underwent endovascular therapy and 45 (37%) underwent bridging therapy. The median scores on mRS at 90 days of the bridging therapy group and the endovascular therapy group were 3 (2–5) and 4 (2–6), with no significant differences (common OR 1.36; 95% CI 0.71 to 2.61). Symptomatic intracranial haemorrhage was reported in three patients who were in the endovascular and bridging therapy groups (relative risk (RR) 1.71; 95% CI 0.36 to 8.12). The mortality between two groups did not differ (RR 0.75; 95% CI 0.37 to 1.54).

Conclusions Our study indicated that endovascular therapy alone might be a viable option for patients with large cerebral infarctions, displaying no noticeable disparity in outcomes compared with bridging therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The effectiveness and safety of endovascular therapy are proven among patients with large cerebral infarct. However, the efficacy of combined therapy with thrombolytic therapy preceding endovascular thrombectomy in these patients remains uncertain.

WHAT THIS STUDY ADDS

⇒ The median modified Rankin Scale scores at 90 days of the endovascular therapy group and the bridging therapy group (intravenous thrombolysis plus endovascular thrombectomy) were not statistically different (common OR 1.36; 95% CI 0.71 to 2.61).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Endovascular therapy alone might be a viable option for patients with large cerebral infarctions.

INTRODUCTION

Recently, two trials conducted in China, the DEVT and DIRECT-MT, suggested that the prognosis of direct thrombectomy was not inferior to that of bridging therapy.[1 2] Conversely, the conclusions drawn were not obtained from the SKIP trial, the SWIFT-DIRECT or MR-CLEAN-NO IV trials.[3–5] DIRECT-SAFE trial, which included Asian and non-Asian populations, did not prove to be inferior to thrombectomy alone compared with bridging therapy.[6] A meta-analysis including the above six trials failed to establish the non-inferiority of endovascular therapy alone when compared with bridging therapy.[7] These studies suggested that endovascular therapy alone might be beneficial in select patients.

Six trials involving large infarct cores have been presented recently.[8–13] The TESLA and LASTE trials were still ongoing.[12 13] The ANGEL-ASPECT (Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core), RESCUE-Japan LIMIT, SELECT 2 and TENSION trials indicated that the utilisation of endovascular therapy yielded better functional outcomes compared with medical care, although three of them being accompanied by vascular complications except TENSION trial among patients with large cerebral infarctions.[8–11] The number needed to treat was 4.94 in SELECT 2 compared with 2.6 in a pooled

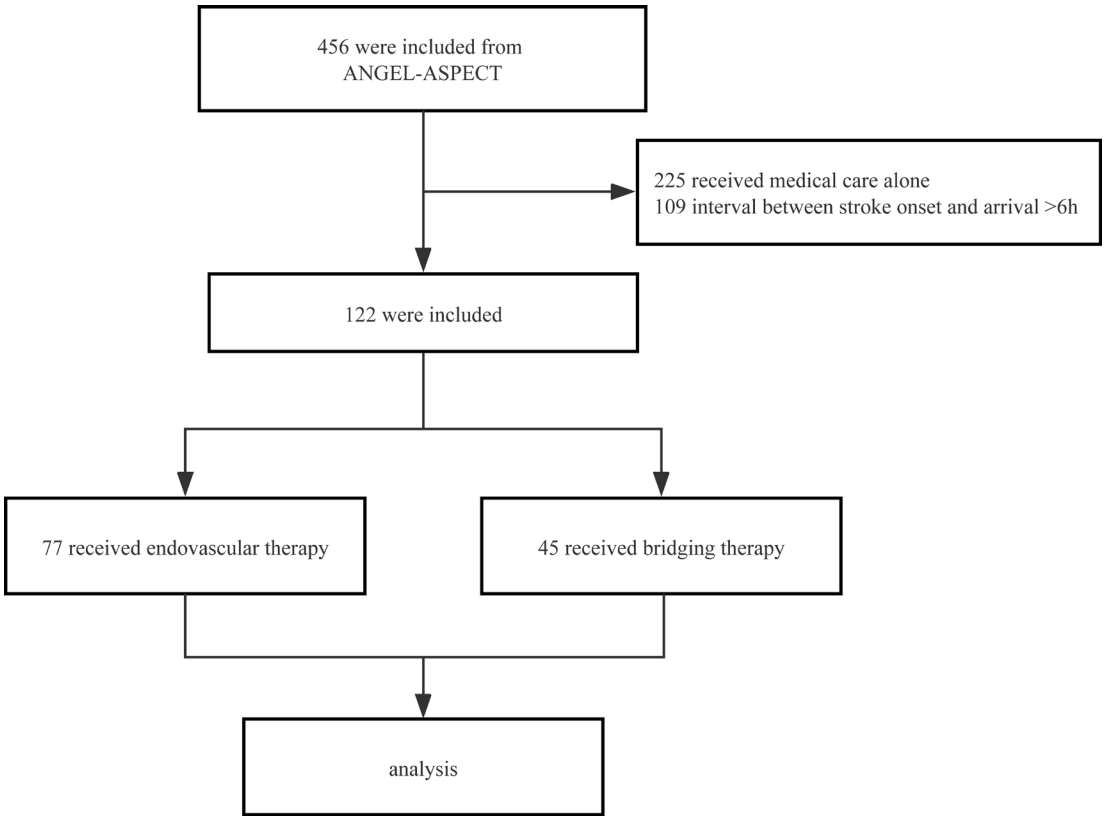

Figure 1 Flow diagram of the patients' selection. ANGEL-ASPECT, Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ClinicalTrials.gov number NCT04551664).

analysis (HERMES), indicating a decreased benefit from endovascular thrombectomy in patients with larger cerebral infarctions.[11 14] Some studies showed that a low Alberta Stroke Program Early CT Score (ASPECTS) value was associated with symptomatic intracranial haemorrhage (sICH), and intravenous thrombolysis (IVT) might increase the haemorrhage risk in patients with a large core infarction.[15 16] A meta-analysis suggested that endovascular thrombectomy was beneficial for patients with acute ischaemic stroke with low ASPECTS despite increased risks of sICH, compared with medical care.[17] Thus, compared with bridging therapy, endovascular therapy alone might be a feasible option for patients with large cerebral infarctions.

Patients with large infarcts were largely excluded from clinical trials, which were decided according to the imaging selection criteria based on the ASPECTS value ≤5 or at the core infarct volume ≥70 mL.[18–20] Some studies evaluated the effect of endovascular treatments alone on the prognosis of patients with large cerebral infarctions, however, obtained conflicting results.[21–24] It has remained controversial whether endovascular therapy alone benefits patients with large cerebral infarctions. Our study was derived from the ANGEL-ASPECT to demonstrate whether endovascular therapy, combined with IVT, was safe and effective in the patients with large infarctions due to cerebral large-vessel occlusion.

METHOD

Design and patient population

A trial of endovascular treatments for acute ischaemic stroke with large cerebral infarctions (ANGEL-ASPECT) as a multicentre, open-label, randomised, blinded-endpoint trial was conducted in 46 hospitals with advanced stroke centres. 456 patients were enrolled from China (ClinicalTrials.gov number, NCT04551664).[10] This clinical trial aimed to elucidate whether endovascular therapy was more effective than medicinal therapy in patients who develop acute large core infarcts secondary to anterior circulation occlusions. The patient eligibility criteria and study methods were reported previously.[25]

Our study was a secondary analysis of ANGEL-ASPECT. All patients undergoing endovascular therapy within 6 hours were eligible for inclusion in this analysis. According to the Chinese guidelines, urokinase thrombolysis can be used in patients within 6 hours of stroke symptom onset.[26] Patients with an onset of less than 4.5 hours received alteplase thrombolytic therapy, while urokinase was a viable option for patients with an onset of less than 6 hours. The reasons or major contraindications for not receiving IVT within 4.5 hours were presented in online supplemental table 1. Neuroimaging inclusion and exclusion criteria were consistent with ANGEL-ASPECT trial.[25] Enrolled patients were divided into (1) the endovascular therapy group (endovascular thrombectomy alone) and (2) the bridging therapy group (IVT plus endovascular

Table 1 Baseline characteristics

Variables	Endovascular therapy (n=77)	Bridging therapy (n=45)	P value
Demographics			
Age (years), mean (SD)	67.5±7.7	67.1±7.8	0.80
Sex (female), n (%)	38 (49.4)	18 (40.0)	0.32
BMI (kg/m^2), mean (SD)	24.3±2.7	25.1±4.6	0.23
Risk factors			
Hypertension, n (%)	53 (68.8)	24 (53.3)	0.09
Diabetes, n (%)	16 (20.8)	8 (17.8)	0.69
Dyslipidaemia, n (%)	3 (3.9)	4 (8.9)	0.42
Current smoker, n (%)	23 (29.9)	8 (17.8)	0.14
Current drinker, n (%)	7 (9.1)	8 (17.78)	0.16
Medical history			
Cerebral infarction, n (%)	14 (18.2)	8 (17.8)	0.96
Atrial fibrillation, n (%)	26 (33.8)	10 (22.2)	0.17
Coronary heart disease, n (%)	12 (15.6)	11 (24.4)	0.23
Stroke subtype			
Atherothrombotic, n (%)	20 (26.0)	10 (22.2)	0.85
Cardioembolic, n (%)	44 (57.1)	26 (57.8)	
Undetermined or other, n (%)	13 (16.9)	9 (20.0)	
Occlusion site*			
ICA, n (%)	29 (37.7)	17 (37.8)	0.74
M1 segment, n (%)	47 (61.0)	28 (62.2)	
M2 segment, n (%)	1 (1.3)	0 (0)	
Interval between stroke onset and arrival			
<4.5 hours, n (%)	54 (70.1)	32 (71.1)	0.91
4.5–6 hours, n (%)	23 (29.9)	13 (28.9)	
ASPECTS value based on CT, n (%)			
0	1 (1.3)	2 (4.4)	0.19
1	7 (9.1)	2 (4.4)	
2	2 (2.6)	4 (8.9)	
3	37 (48.1)	16 (35.6)	
4	21 (27.3)	11 (24.4)	
5	9 (11.7)	10 (22.2)	
NIHSS score at admission, median (IQR)	17 (14–20)	18 (13–20)	0.83
Median infarct core volume, mean (SD)†	67.0±40.0	61.6±37.6	0.52

*M1 segment indicates the middle cerebral artery horizontal or sphenoidal segment; M2 segment indicates the middle cerebral artery insular segment.
†The definition of infarct core was an area with an apparent diffusion coefficient ≤620×10^{-6} mm^2/s on MRI or a relative cerebral blood flow below 30% on CT perfusion.
ASPECTS, Alberta Stroke Program Early CT Score; BMI, body mass index; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale.

thrombectomy), according to their treatments received after experiencing an acute ischaemic stroke.

Outcomes

The primary outcome: ordinal modified Rankin Scale (mRS) at 90 days. Secondary outcomes: (1) an mRS of 0–2 and 0–3 at 90 days; (2) score of 0–1 on National Institutes of Health Stroke Scale (NIHSS) or a ≥10-point increase in NIHSS score within 36 hours[10]; (3) the alteration in volume of infarct core from baseline diffusion-weighted imaging or CT perfusion imaging to MRI at 36 hours or to CT at 7 days or upon discharge; and (4) recanalisation of occluded artery at 36 hours. Safety outcomes: (1) intracranial haemorrhage within 2 days; (2) sICH (an increase of ≥4 points in total NIHSS compared with immediately before worsening or an increase of ≥2 points in one NIHSS subcategory, with any intracranial haemorrhage on imaging) within 2 days[27]; (3) mortality within 90 days following ischaemic stroke onset; and (4) decompressive hemicraniectomy during hospitalisation. The

Table 2 Comparison of outcome parameters between endovascular therapy alone and bridging therapy

Outcomes	Endovascular therapy (n=77)	Bridging therapy (n=45)	Treatment effect* (95% CI)	P value
Primary outcome				
mRS score at 90 days	4 (2–6)	3 (2–5)	1.36 (0.71 to 2.61)	0.35
Secondary outcomes				
mRS score at 90 days, n (%)				
0–2	21 (27.3)	16 (35.6)	1.30 (0.76 to 2.23)	0.34
0–3	33 (42.9)	23 (51.1)	1.19 (0.81 to 1.75)	0.38
NIHSS 0–1 or improved ≥10 points at 36 hours, n (%)	6 (7.8)	2 (4.4)	0.57 (0.12 to 2.71)	0.47
Change from baseline in infarct core volume, mean (SD)	87.4±91.3	111.4±119.5	24.02 (–14.09 to 62.13)	0.21
Target artery recanalisation at 36 hours, n (%)	60 (90.9)	32 (86.5)	0.95 (0.82 to 1.1)	0.49
Safety outcomes				
Symptomatic intracranial haemorrhage within 2 days, n (%)	3 (3.9)	3 (6.7)	1.71 (0.36 to 8.12)	0.50
Any intracranial haemorrhage within 2 days, n (%)	34 (44.2)	23 (51.1)	1.16 (0.79 to 1.69)	0.46
Death within 90 days, n (%)	24 (31.2)	11 (24.4)	0.75 (0.37 to 1.54)	0.43
Decompressive hemicraniectomy during hospitalisation, n (%)	3 (3.9)	6 (13.3)	3.42 (0.9 to 13.02)	0.06

*Treatment effects are reported including the primary outcome as a cOR for the ordinal shift on the mRS; the safety outcome of death as an HR; the secondary outcomes of alteration in the volume of infarct core as the mean difference; and the remaining outcomes as the RR.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

detail of the outcome definitions was shown in online supplemental table 2.

Subgroups were defined according to interval between symptom onset and arrival (<4.5 hours vs 4.5–6 hours), stroke subtype classification (large artery atherosclorosis, cardioembolic stroke and other), NIHSS score at admission (<16 vs ≥16 points) and infarct core volume (<70 mL vs ≥70 mL). Subgroup analyses were conducted to assess the relative risks (RRs) of achieving favourable functional outcomes (mRS ≤2) at 90 days among patients receiving endovascular therapy compared with those undergoing bridging therapy.

Statistical analysis

Continuous variables were expressed as mean±SD or as a median with IQR,while categorical variables were reported as frequencies and percentages. Baseline characteristics were compared using X^2 test or Fisher's exact test for categorical variables, and the Student's t-test or Wilcoxon-Mann-Whitney test for continuous variables. Ordinal logistic regression was conducted to compare the primary endpoint between the two groups, and the common OR (cOR) with 95% CI was calculated for the ordinal shift in the distribution of mRS scores towards a favourable outcome. A general linear regression was used to estimate the alteration from baseline in regard to volume of infarct core as the mean difference and 95% CI. A Cox proportional-hazards model was conducted to evaluate the HR with 95% CI between the two groups for the outcome of mortality within 90 days. The Cochran-Mantel-Haenszel test was performed to compare secondary endpoints and other safety outcomes

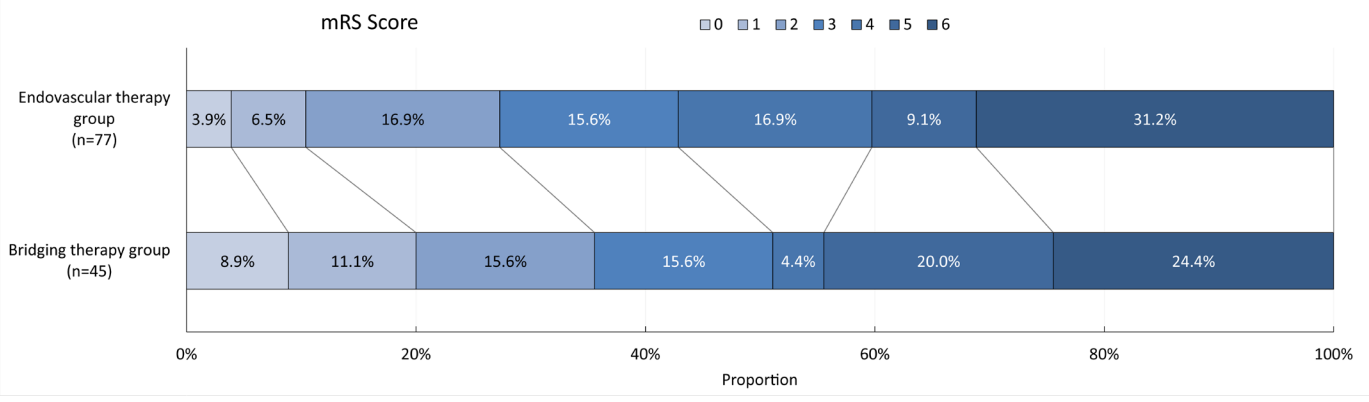

Figure 2 Distribution of scores on the modified Rankin Scale (mRS) at 90 days among patients presenting with a large infarct core.

Table 3 Subgroup analyses of the outcome parameters

Subgroup*	Endovascular therapy	Bridging therapy	RR (95% CI)	P value	P for interaction
Overall	77	45			
Interval between stroke onset and arrival					0.10
<4.5 hours	14/54 (25.9)	14/32 (43.8)	1.69 (0.93 to 3.07)	0.09	
4.5–6 hours	7/23 (30.4)	2/13 (15.4)	0.51 (0.12 to 2.08)	0.32	
Stroke subtype					0.16
Atherothrombotic	6/20 (30.0)	4/10 (40.0)	1.33 (0.48 to 3.67)	0.59	
Cardioembolic	10/44 (22.7)	11/26 (42.3)	1.86 (0.92 to 3.77)	0.09	
Undetermined or other	5/13 (38.5)	1/9 (11.1)	0.29 (0.04 to 2.08)	0.17	
NIHSS score at admission					0.75
<16	13/30 (43.3)	9/18 (50.0)	1.15 (0.62 to 2.14)	0.66	
≥16	8/47 (17.0)	7/27 (25.9)	1.52 (0.62 to 3.74)	0.36	
Infarct core volume					0.78
<70 mL	15/43 (34.9)	12/26 (46.2)	1.32 (0.74 to 2.37)	0.36	
≥70 mL	6/34 (17.7)	4/19 (21.1)	1.19 (0.38 to 3.71)	0.76	

*The outcome parameter of the subgroup analysis was the score of mRS ≤2.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RR, relative risk.

between the two groups, and the 95% CI of RRs was calculated. The same models were used for the subgroup analyses of the incidence of mRS ≤2, including the time of interval between symptom onset and arrival (<4.5 hours vs 4.5–6 hours), stroke subtype (large artery atherosclerosis, cardioembolic stroke and other), NIHSS score at admission (<16 vs ≥16 points) and infarct core volume (<70 mL vs ≥70 mL). Besides this, the subgroup analysis did not adjust for other variables. All statistical tests were two tailed at α of 0.05 level for significance. Analyses were conducted by using Statistical Analysis System V.9.4 (SAS Institute).

RESULTS

The ANGEL-ASPECT Study enrolled 456 patients who suffered from anterior circulation acute ischaemic stroke and sustained a large infarction. From this analysis, 334 patients were excluded, predominantly patients receiving only medical treatment (n=225) or if symptom onset up until hospital presentation was >6 hours (n=109). The remaining 122 patients were enrolled in this study, of whom 77 received endovascular therapy and 45 received bridging therapy (figure 1). There were numerical differences between the two groups in hypertension (15.5%), current smoking (12.1%), atrial fibrillation (11.6%) and baseline ASPECTS distribution, but these differences were not statistically significant at baseline, as shown in table 1. Among the included subjects, 30 patients (24.6%) were classified as large artery atherosclerosis type according to the stroke subtype, 70 patients (57.4%) suffered from an embolic stroke and 22 cases (18.0%) were attributed to other causes. Most patients (70.5%) arrived at the hospital within 4.5 hours of symptom onset (table 1).

The outcomes of the two groups are presented in table 2, online supplemental table 3 and figure 2. In the primary outcome analysis, the median mRS scores at 90 days of the endovascular therapy group and the bridging therapy were 4 and 3 (cOR 1.36; 95% CI 0.71 to 2.61). As for the secondary outcome, the rate of patients with an mRS score of 0–2 at 90 days was 27.3% in the endovascular therapy group and 35.6% in the bridging therapy group (RR 1.30; 95% CI 0.76 to 2.23). The rate of patients with an mRS score of 0–3 at 90 days was 42.9% in the endovascular therapy group and 51.1% in the bridging therapy group (RR 1.19; 95% CI 0.81 to 1.75). No significant difference was identified in the NIHSS 0–1 or improved ≥10 points, change from baseline in the volume of infarct core or target artery recanalisation between the two groups. As for the safety outcomes, the rate of any intracranial haemorrhage was 44.2% and 51.1%, respectively, in the endovascular therapy group, as well as in the bridging therapy group (RR 1.16; 95% CI 0.79 to 1.69). sICH occurred in three patients (3.9%) in the endovascular group and in three patients (6.7%) in the bridging therapy group (RR 1.71; 95% CI 0.36 to 8.12). The count of deaths within 90 days was 24 (31.2%) in the endovascular therapy group and 11 (24.4%) in the bridging therapy group. The percentage of decompressive hemicraniectomy during hospitalisation was 13.3% and 3.9% in the bridging therapy group and in the endovascular therapy group, respectively (RR 3.42; 95% CI 0.90 to 13.02). Overall, the safety outcomes did not statistically differ between two groups. Online supplemental tables 4 and 5 showed the outcomes after adjusting for covariates.

Regarding subgroup analysis, no interaction was found between endovascular therapy or bridging therapy and

other risk factors (table 3). Among patients with stroke symptom onset to hospital arrival time <4.5 hours, the percentage of patients with good prognosis, who received bridging therapy, was higher than that of the endovascular therapy group (43.8% vs 25.9%); however, there were no significant differences. Moreover, there were also no significant statistical differences in the main outcomes of the two treatment strategies among patients with different aetiologies, baseline NIHSS scores or infarct core volumes.

DISCUSSION

In this secondary analysis, we investigated the benefits and risks of thrombolytic therapy before endovascular thrombectomy in patients with large infarct volumes from ANGEL-ASPECT. Our research suggested that there were no significant statistical differences in the rate of 90-day favourable outcomes (mRS ≤2) and target artery recanalisation between endovascular therapy alone and bridging therapy. Moreover, there was no difference in statistical significance between the two groups in relation to safety outcomes.

Recently, the ANGEL-ASPECT trial, RESCUE-Japan LIMIT trial and SELECT 2 trial have demonstrated that endovascular treatment can improve outcomes of patients who had an acute ischaemic stroke with large cerebral infarctions but showed more risks in intracranial haemorrhages, defined by an ASPECTS value of 5 or less.[8 10 11] Broocks *et al*[23] included patients with ASPECT scores of 0–5 from the GSR-ET trial and three additional tertiary stroke centres. They found that the incidence of sICH was lower in patients with endovascular therapy compared with those undergoing bridging therapy (6.4% vs 17.8%). Similarly, according to an explorative analysis of the BEYOND-SWIFT, which divided patients into three baseline ASPECTS groups (0–5, 6–8 and 8–10), in the strata of ASPECTS of 0–5, the risk of sICH was elevated in patients who underwent IVT before endovascular thrombectomy, compared with those who did not underwent IVT (adjusted OR 6.31; 95% CI 1.87 to 21.29).[28] The studies above suggested that IVT, before endovascular thrombectomy, might increase the risk of sICH, compared with the endovascular thrombectomy in patients with large cerebral infarctions.

Our study did not demonstrate any significant difference in the rate of favourable outcomes (mRS ≤2) at 90 days and sICH within 48 hours between endovascular therapy alone and bridging therapy. Several other studies have reported similar results.[21 22] Anadani *et al*[22] conducted a research on patients with ASPECTS value ≤5 who underwent thrombectomy in the STAR trial. They used the propensity score matching method and found that the favourable outcomes (90-day mRS 0–2) and successful reperfusion rates were comparable between patients who underwent IVT and those who did not. The incidence of intracerebral haemorrhage was also comparable between two groups in the original cohort and the matched cohort (42.3% vs 41.4%, p=0.85; 42.1% vs 38.6%, p=0.59). A subgroup analysis of the DIRECT-MT trial was conducted, which divided patients into baseline ASPECTS subgroups: 0–4 (n=56, 8.6%), 5–7 (n=164, 25.3%) and 8–10 (n=429, 66.1%).[21] The study found that baseline infarct volume did not influence the effect of IVT before endovascular therapy with respect to better functional outcomes or adverse events. Another subanalysis of RESCUE-Japan LIMIT, enrolling patients with value of 3–5 on ASPECTS, suggested that the efficacy between endovascular therapy alone and bridging therapy did not statistically differ, while IVT before endovascular therapy might increase sICH risk.[24] Broocks *et al* suggested that patients who underwent direct endovascular therapy had a lower mRS score at 90 days compared with those who received bridging therapy, while the difference was not statistically significant.[23]

Additionally, our study had certain limitations. First, it was conducted as a post hoc analysis; thus, this observational study can only document associations, not causative relations. Furthermore, the limited sample size in our analysis may have influenced the results, necessitating caution when interpreting the findings. Third, our study followed the guideline for thrombolysis in China. Patients who had an onset time of 4.5–6 hours also received urokinase, which means that conclusions drawn from this study may not be applicable to countries that exclusively use alteplase for IVT.

CONCLUSIONS

Endovascular therapy alone, in patients with large cerebral infarctions, achieves a similar favourable functional outcome compared with bridging therapy, without increasing haemorrhagic events. Future research is warranted to assess the efficacy and safety of endovascular therapy alone in patients with large cerebral infarctions.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The ANGEL-ASPECT trial involves human participants and was approved by the Ethics Committee at Beijing Tiantan Hospital (IRB approval number: KY2020-072-02) and all participating centres. All the participants, or their legal representatives, provided informed consent prior to enrolment.

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