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Endovascular treatment with or without intravenous alteplase for acute ischaemic stroke due to basilar artery occlusion

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ABSTRACT

Background and purpose It remains controversial if endovascular treatment (EVT) can improve the outcome of patients with acute basilar artery occlusion (BAO). This study aims to compare the functional outcomes between EVT with and without intravenous thrombolysis (IVT) first in patients who had acute ischaemic stroke (AIS) due to BAO.

Methods Patients who had AIS with BAO who underwent EVT within 24 hours of onset were enrolled in this multicentre cohort study, and the efficacy and safety were compared between IVT+EVT and direct EVT. The primary outcome was 90-day functional independence. All outcomes were assessed with adjusted OR (aOR) from the multivariable logistic regression. In addition, a meta-analysis was performed on all recently published pivotal studies on functional independence after EVT in patients with BAO.

Results Of 310 enrolled patients with BAO, 241 (78%) were treated with direct EVT and 69 (22%) with IVT+EVT. Direct EVT was associated with a worse functional outcome (aOR, 0.46 (95% CI 0.24 to 0.85), p=0.01). IVT+EVT was associated with a lower percentage of patients who needed ≥3 passes of stent retriever (10.14% vs 20.75%). The meta-analysis regression revealed a potential positive correlation between bridging with IVT first and functional independence (r=0.14 (95% CI 0.05 to 0.24), p<0.01).

Conclusions This study showed that compared with direct EVT, EVT with IVT first was associated with better functional outcomes in patients with BAO treated within 24 hours of onset. The meta-analysis demonstrated similar favourable efficacy of IVT first followed by EVT in patients with BAO.

INTRODUCTION

Basilar artery occlusion (BAO) accounts for about 2% of all stroke cases and has a high mortality rate and risk of disability, even after successful recanalisation.[1 2] Reperfusion therapy might improve the prognosis of patients with BAO but with very limited evidence.[3]

Pivotal randomised controlled trials (RCTs) confirmed that patients who had acute ischaemic stroke (AIS) with anterior-circulation large vessel occlusion (LVO) could benefit from intravenous thrombolysis (IVT) and endovascular treatment (EVT) up to 24 hours from stroke onset.[4] Safety of EVT in patients with BAO has been proven in recent two RCTs. However, the efficacy of EVT was not superior to that of medical treatment in patients with BAO by the current evidence. Only one cohort study found that EVT had a marginal effect on improving functional outcomes.[5–7] Most centres apply recanalisation therapies for BAO up to 12–24 hours after symptom onset, which is a substantially longer time window than the 6 hours recommended by current guidelines.[8]

Recent RCTs indicated that direct endovascular treatment (DEVT) was non-inferior to bridging treatment within 4.5 hours of onset in patients who had AIS with an anterior-circulation LVO.[9 10] However, the specific effect of IVT first followed by EVT in patients with posterior-circulation LVO remains unclear. The proportion of prior IVT ranged from 18.4% to 78.4% in the reported BAO trials,[5–7] which is much lower than in the anterior-circulation LVO trials (approximately 80%).[4] A recently published subgroup analysis of the Basilar Artery International Cooperation Study (BASICS) illustrated that the efficacy of EVT was marginally better with bridging therapy in patients with BAO (OR, 1.16–2.70 (95% CI 0.88 to 8.11) vs 1.08 (95% CI 0.53 to 2.23)), but without statistical significance.[5]

The initial onset of BAO is usually insidious and often progresses rapidly. Owing to the different degrees of involvement of the brainstem, patients with BAO can present with symptoms that vary from isolated cranial nerve palsies or hemiplegia to a locked-in state or coma. Even small infarcts would often result in poor outcomes. Moreover,

the collateral compensatory ability of the perforating branches of the basilar artery is worse than that of the anterior-circulation large vessels. Therefore, patients with BAO have more irreversible and severe infarction, and even with successful recanalisation, reperfusion therapy in BAO often fails to improve disability. Furthermore, in some patients with BAO with intracranial stenoses and tortuous vessels in the vertebrobasilar artery system, EVT becomes more difficult. Hence, clinical assessment and therapeutic options for BAO are different from that of anterior-circulation occlusions.

This study investigates the functional outcomes of IVT+EVT and DEVT in patients who had AIS due to BAO in the real world.

METHODS

This prospective cohort study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11]

Study design and setting

Details of the Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization (RESCUE-RE) have been reported previously.[12] Briefly, RESCUE-RE is an ongoing, investigator-initiated, nationwide, prospective, observational cohort study recruiting patients who had acute stroke with an LVO who received EVT at 18 comprehensive stroke centres across China. Details on demographic features, clinical variables and laboratory data were collected by trained research coordinators and investigators. All imaging files were stored in a centralised manner and reviewed independently by two radiologists (WGu and XHo) blinded to the clinical data. All records at each participating centre were examined and audited by full-time quality control coordinators.

Participants and treatments

From July 2018 to October 2020, patients who had AIS treated with EVT within 24 hours of stroke onset in RESCUE-RE and who met the following criteria were recruited to the current study: (1) age >18 years old; (2) AIS diagnosed based on brain imaging with documented LVO in the basilar artery, which was confirmed by either a CT angiography or magnetic resonance angiography or digital subtraction angiography (DSA), and patients with occluded distal intracranial vertebral artery (V4 segment) resulting in no flow to the basilar artery (eg, functional BAO); (3) IVT was initiated within 4.5 hours according to the standard criteria in qualified patients; (4) a prestroke modified Rankin Scale (mRS) score ≤2; and (5) followed up for 3 months.

All patients were admitted to the intensive care unit at the participating centre, and periprocedural management was conducted according to the local clinical care protocols and latest national guideline.[8] IVT was given with a standard dosage of alteplase (0.9 mg/kg over 1 hour with a 10% initial bolus, maximum 90 mg). Alteplase infusion should be completed during EVT, even if the procedure was successful in establishing revascularisation. Mechanical thrombectomy, aspiration, balloon angioplasty, stent implantation and combination therapies (two or more of the above procedures) were all considered as a form of EVT.

Variables and outcome measurement

The study variables were collected prospectively, including baseline characteristics, details of workflow, EVT procedure, perioperative treatment, and primary and secondary outcomes. National Institutes of Health Stroke Scale (NIHSS) score on admission was used to assess stroke severity. BAO was divided into distal, middle and proximal BAO based on the occlusion site. The posterior-circulation collateral status was assessed using both the Basilar Artery on Computed Tomography Angiography (BATMAN) score and the Posterior Circulation Collateral Score (PC-CS).[13] Successful pre-EVT or post-EVT reperfusion was defined as a score of ≥2b on the modified Thrombolysis in Cerebral Ischemia (mTICI) scale on DSA. Patients were followed up for 3 months through face-to-face or over-the-phone communications by staff who were blinded to patient information and treatment.

The primary outcome was functional independence, defined as a dichotomised mRS score of 0–2 at 90 days. The secondary outcomes included mortality, successful reperfusion, culprit vessel occlusion at 24 hours after EVT, any intracranial haemorrhage (ICH) and symptomatic intracranial haemorrhage (sICH). sICH was defined as any ICH on post-EVT cerebral imaging with an increase of ≥4 points on the NIHSS within 7 days, according to the Second European-Australasian Acute Stroke Study criteria.[14]

Statistical analysis

Categorical variables were presented as numbers (proportions) and continuous variables as median (IQR) or mean±SD. χ^2 test or Fisher's exact test was used for univariate analysis of categorical variables. Continuous variables were analysed with Student's t-test or Mann-Whitney U test. Multivariate logistic regression was performed to obtain the OR and 95% CI of the associations between the two groups and their outcomes. The mRS scores of patients treated with IVT+EVT were compared with those of patients treated with DEVT by conducting ordinal logistic regression to obtain the common OR. Potential confounders were adjusted based on the results of univariable analyses to $p<0.05$ while taking into consideration the important risk factors in combination with clinical judgement and expert knowledge: age, baseline NIHSS score, onset to puncture time, prestroke mRS score, history of stroke and transient ischaemic attack. The functional outcomes in subgroups were divided based on age, baseline NIHSS score, key intervals and other key variables and were compared between two groups. Univariate logistic regression was applied to calculate the OR in all subgroups.

Meta-analysis

Only randomised trials or high-quality cohort studies in recent years that reported original data on functional independence (mRS score of 0–2 at 90 days) after EVT in patients with BAO plus the current cohort study were included in this meta-analysis. The occurrence of the following events in the EVT group was extracted and analysed: total patients, treated with IVT, an mRS score of 0–2 and deceased patients at 90 days (the IVT+EVT group and the DEVT group of RESCUE-RE were analysed separately). To combine the data from all studies, the restricted maximum likelihood random-effects method was used to estimate a summary across all included studies. The percentage of mRS score of 0–2 estimates and the associated 95% CI for each of the endpoints were calculated. Between-study heterogeneities were evaluated by the I^2 statistics and the Cochran Q (χ^2) statistics, with a p value of 0.10 set to be significant for heterogeneity. The results of the meta-analysis regression would demonstrate the influence of IVT on functional independence in each study as well as the overall meta-analysis summary estimate.

All analyses were performed with SAS V.9.4 and Stata V.16.0 software. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Participants

From July 2018 to October 2020, 1701 patients were consecutively enrolled in the RESCUE-RE cohort. A total of 321 patients met the inclusion criteria and were included in the current study (figure 1). After excluding 11 patients who were lost to follow-up, 310 patients were eligible for the final analysis, with 241 (78%) treated with DEVT and 69 (22%) with IVT+EVT. Patients were allocated to the DEVT group (241 patients) if they did not receive IVT first. The reasons for withholding IVT included contraindications to IVT, beyond the treatment time window, over 4.5 hours of in-hospital delay, refusal by patients or their families, and other reasons.

Baseline characteristics

Table 1 shows the baseline characteristics of the participants in the two groups. The mean age was 61.39±10.92 years and 77% of the participants were male. The median NIHSS score was 21 (IQR 11–27). The median BATMAN score was 6 (IQR 4–7) and the PC-CS was 5 (IQR 2–6). V4 occlusion was found in 36.13% of the patients and BAO in 63.87%, including 31.94% in the middle segment. As for the aetiology, 80.97% were from atherosclerosis, 14.19% were cardioembolic and 15% were of other types. The baseline characteristics of the participants in the two treatment groups were similar.

Workflow intervals and EVT procedures

The median onset to needle time in the IVT+EVT group was 190 min (160–233). The median onset to arrival time was 293 min (135–520). The onset to puncture time was 485 min (333–835); the puncture to recanalisation time was 122 min (78–175); and the onset to recanalisation time was 630 min (457–1012). There was no difference in the time interval parameters between the two groups. Thrombectomy was a little more common in the DEVT group, with statistical significance (86.72% vs 76.81%, p=0.04). In addition, in the DEVT group, more patients received combination therapy (53.53% vs 39.13%,

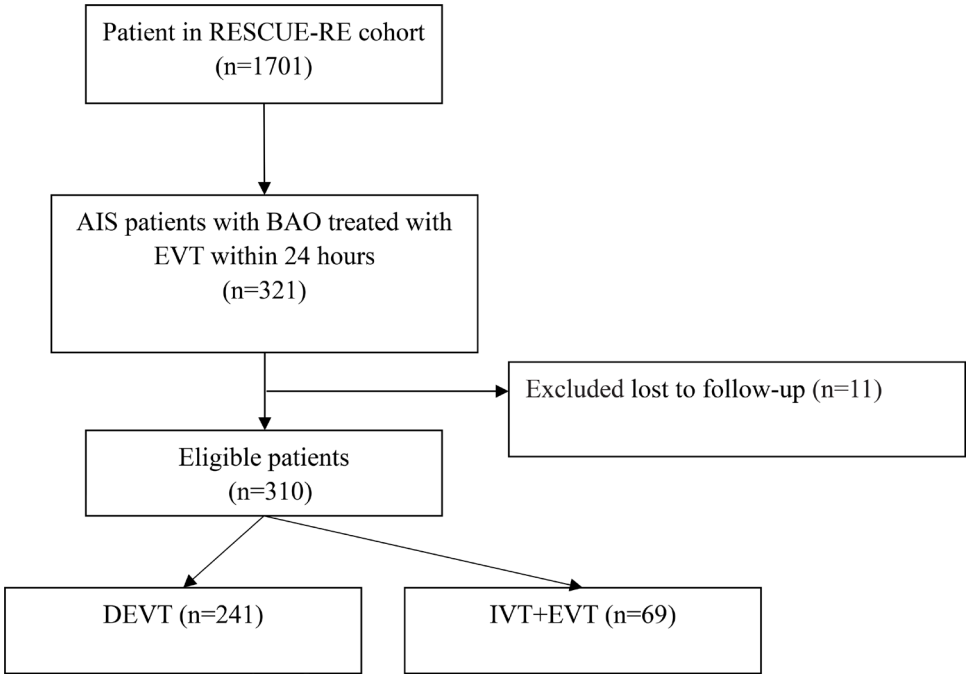

Figure 1 Flow chart of the current cohort study. AIS, acute ischaemic stroke; BAO, basilar artery occlusion; DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; RESCUE-RE, Registration Study for Critical Care of Acute Ischemic Stroke After Recanalization.

Table 1 Baseline characteristics of patients treated with DEVT vs IVT+EVT

Baseline characteristics	Total (N=310)	DEVT (n=241)	IVT+EVT (n=69)	P value
Age, mean±SD, years	61.39±10.92	61.63±11.40	60.54±9.11	0.29
Male, n (%)	240 (77.42)	186 (77.18)	54 (78.26)	0.85
B-NIHSS, median (IQR)	21 (11–27)	21 (12–27)	20 (9–27)	0.68
Medical history, n (%)				
Atrial fibrillation	30 (9.68)	20 (8.30)	10 (14.49)	0.12
Stroke/TIA	80 (25.81)	67 (27.80)	13 (18.84)	0.13
CHD/MI	35 (11.29)	30 (12.45)	5 (7.25)	0.23
Hypertension	217 (70.00)	167 (69.29)	50 (72.46)	0.61
Diabetes	70 (22.58)	56 (23.24)	14 (20.29)	0.61
Currently smoke	142 (45.81)	107 (44.40)	35 (50.72)	0.35
Previous antiplatelets, n (%)	70 (22.58)	60 (24.90)	10 (14.49)	0.07
Previous anticoagulant, n (%)	10 (3.23)	8 (3.32)	2 (2.90)	0.86
Occlusion location, n (%)				0.74
Distal BA	42 (13.55)	30 (12.45)	12 (17.39)	
Middle BA	99 (31.94)	78 (32.37)	21 (30.43)	
Proximal BA	57 (18.39)	44 (18.26)	13 (18.84)	
V4	112 (36.13)	89 (36.93)	23 (33.33)	
PC-ASPECT, median (IQR)	6 (5–8)	6 (5–8)	5 (4–7)	0.08
BATMAN, median (IQR)	6 (4–7)	6 (3–7)	6 (4–7)	0.36
PC-CS, median (IQR)	5 (2–6)	5 (2–6)	5 (3–7)	0.14
Stroke aetiology, n (%)				0.92
Atherosclerotic	251 (80.97)	194 (80.50)	57 (82.61)	
Cardioembolic	44 (14.19)	35 (14.52)	9 (13.04)	
Other	15 (4.84)	12 (4.98)	3 (4.35)	
General anaesthesia, n (%)	208 (70.27)	164 (70.69)	44 (68.75)	0.76

P value for comparison between patients with DEVT and IVT+EVT treatment.
BA, basilar artery; BATMAN, Basilar Artery on Computed Tomography Angiography; B-NIHSS, Baseline National Institutes of Health Stroke Scale; CHD, coronary heart disease; DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; MI, myocardial infarction; PC-ASPECT, Posterior Circulation Alberta Stroke Program Early Computed Tomography Score; PC-CS, Posterior Circulation Collateral Score; TIA, transient ischaemic attack.

p<0.01), and the proportion of patients with ≥3 retriever passes (20.75% vs 10.14%, p=0.05) was marginally higher. The median residual stenosis after EVT was 20%. No difference was found in workflow and procedures between the two groups (table 2).

Primary and secondary outcomes

Analysis of the primary outcome revealed fewer patients with an mRS score of 0–2 at 90 days in the DEVT group after adjusting for potential confounders (aOR, 0.46 (95% CI 0.24 to 0.85), p=0.01). The distributions (shift) of mRS score at 90 days (figure 2) differed between the two groups after the adjustment (adjusted common odds ratio (acOR), 0.56 (95% CI 0.34 to 0.90), p=0.02).

The primary and secondary outcomes are presented in table 3. Successful reperfusion after EVT, the culprit vessel occlusion at 24 hours, and the frequency of any ICH and sICH were not statistically different between the DEVT group and the IVT+EVT group. Mortality at 90 days was marginally higher in patients treated with DEVT (26.14% vs 18.84%), without statistical significance (aOR, 1.79 (95% CI 0.87 to 3.71), p=0.11).

Subgroup analysis

The subgroup analyses (figure 3) did not show any characteristics significantly associated with treatment effect, except for patients with baseline NIHSS score of 10–21. In this subgroup with an NIHSS score between 10 and 21 (96 patients, 32.11% of the total subjects), the 90-day functional outcome was better in the IVT+EVT group compared with the DEVT group (OR, 0.15 (95% CI 0.05 to 0.48), p interaction=0.04). Patients of younger age (≤75 years), with atherosclerotic stroke, with shorter time interval from onset to door (≤3 hours), to groin puncture (≤6 hours) and to recanalisation (≤12 hours), and with baseline NIHSS score ≤21, BATMAN score >7, PC-CS >5 or direct to EVT centre had better outcomes in the IVT+EVT group, although without statistical significance.

Table 2 Characteristics of the workflow and EVT procedure

Variable	Total (N=310)	DEVT (n=241)	IVT+EVT (n=69)	P value
Time intervals, median (IQR), min				
Onset to needle	–	–	190 (160–233)	–
Onset to puncture	485 (333–835)	470 (320–875)	510 (378–763)	0.50
Puncture to recanalisation	122 (78–175)	122 (85–175)	122 (60–185)	0.37
Onset to recanalisation	630 (457–1012)	626 (450–1070)	641 (497–885)	0.66
Details of EVT procedure, n (%)				
Thrombectomy	262 (84.52)	209 (86.72)	53 (76.81)	0.04
IAT	41 (13.23)	31 (12.86)	10 (14.49)	0.72
Balloon angioplasty	126 (40.65)	99 (41.08)	27 (39.13)	0.77
Stenting	93 (30.00)	77 (31.95)	16 (23.19)	0.16
Combined	156 (50.32)	129 (53.53)	27 (39.13)	0.04
≥3 passes	57 (18.39)	50 (20.75)	7 (10.14)	0.05
Residual stenosis, mean±SD, %	20.78±24.4	20.92±23.71	20.30±26.93	0.46

P value for comparison between patients treated with DEVT and bridging treatment.
DEVT, direct endovascular treatment; EVT, endovascular treatment; IAT, intra-arterial thrombolysis; IVT, intravenous thrombolysis.

Meta-analysis

A total of two randomised trials and two cohort trials,[5–7] including RESCUE-RE, with 1176 patients were eligible for the meta-analysis (online supplemental figure S1). In the other three trials, EVT was not considered an inclusion criterion, but as an intervention, and for these three trials the original data needed for the current analysis were extracted from the EVT group.[5–7] The average duration of follow-up was 90 days. The mean duration from onset to treatment was 246–485 min and the NIHSS score at baseline was between 21 and 32. The proportion of IVT first ranged from 18.4% to 78.4%. More details on the design, characteristics and quality assessment of the included trials are provided in online supplemental tables S1 and S2. After EVT, 31.2% (95% CI 26.0 to 36.4) of the patients had functional independence (mRS score 0–2 at 90 days), while the mortality rate was between 18.9% and 46.2%. Successful reperfusion (mTICI ≥2b) after EVT was achieved in 68.1%–80.7% of the patients. About 4.5%–8.7% of the patients had sICH (table 4, figure 4A).

A stratified analysis by onset to EVT time (<24 hours and <8 hours) is provided in online supplemental figure S2. Of the patients, 30.40% (95% CI 22.13 to 38.68) had functional independence in the subgroup of onset to EVT time <24 hours, while the functional independence rate was 34.46% (95% CI 28.17 to 40.76) in the subgroup of onset to EVT time <8 hours. There was substantial heterogeneity in the overall analysis (I^2=82.10%), but there was no statistical difference between the two subgroups (p=0.44). The meta-analysis regression model (figure 4B) revealed significant positive correlation between the proportion of patients who had IVT first and functional independence after EVT (r=0.14 (95% CI 0.05 to 0.24), p<0.01). There was also no significant publication bias detected with regard to functional independence on examination of funnel plots (online supplemental figure S3).

DISCUSSION

Previous studies had inconclusive and conflicting conclusions regarding the comparison between EVT and

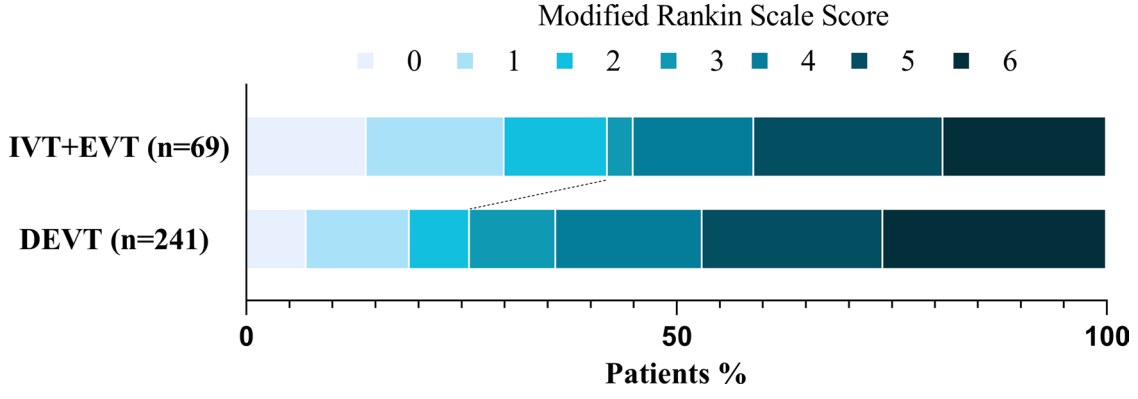

Figure 2 Distribution of mRS score at 90 days. DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale.

Table 3 Univariate and multivariate analyses for the primary and secondary outcomes

Variable, n (%)	DEVT (n=241)	IVT+EVT (n=69)	OR	P value	aOR*	P value*
Primary outcome						
mRS 0–2 at 90 days	63 (26.14)	29 (42.03)	0.49 (0.28 to 0.85)	0.01	0.46 (0.24 to 0.85)	0.01
Secondary outcome						
Mortality at 90 days	63 (26.14)	13 (18.84)	1.52 (0.78 to 2.97)	0.21	1.79 (0.87 to 3.71)	0.11
Occlusion at 24 hours	58 (24.07)	11 (15.94)	1.67 (0.82 to 3.40)	0.16	1.38 (0.68 to 2.79)	0.37
mTICI ≥2b post-EVT	181 (75.10)	47 (68.12)	1.41 (0.79 to 2.53)	0.25	1.50 (0.82 to 2.77)	0.19
Any ICH	50 (20.75)	12 (17.39)	1.24 (0.62 to 2.49)	0.54	1.18 (0.58 to 2.39)	0.65
sICH	21 (8.71)	5 (7.25)	1.22 (0.44 to 3.36)	0.70	1.17 (0.41 to 3.30)	0.77

P value for comparison between patients treated with DEVT and bridging treatment.
*Adjusted for age, baseline NIHSS score, prestroke mRS score, history of stroke/TIA and onset to puncture.
aOR, adjusted OR; DEVT, direct endovascular treatment; EVT, endovascular treatment; ICH, intracranial haemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction Score; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial haemorrhage; TIA, transient ischaemic attack.

standard medical treatment in patients who had AIS due to BAO.[5–7] A recent RCT revealed that EVT and medical therapy were not significantly different in achieving favourable functional outcome in patients with BAO.[5] However, a cohort registry trial, the EVT for Acute Basilar Artery Occlusion Study, indicated that EVT provided considerable benefit compared with standard medical care alone in patients with BAO (aOR, 3.08 (95% CI 2.09 to 4.55), p<0.01).[7] DEVT was known to be non-inferior to bridging treatment within 4.5 hours of onset in patients who had AIS with anterior-circulation LVO.[9 10] However, data comparing IVT+EVT and DEVT in patients with BAO are scarce. As the first multicentre cohort study comparing the effectiveness and safety of IVT+EVT versus DEVT in patients with BAO treated within 24 hours of onset, our study found that the combination of EVT with IVT first (bridging) was associated with a better clinical outcome. Moreover, the regression meta-analysis identified a potential positive correlation between the proportion of patients with bridging treatment and improved functional independence in patients with BAO. Our study therefore provided more data and evidence to support the use of bridging treatment.

There is no consensus about the time window to begin EVT in BAO. Although current guidelines suggest that EVT within 6 hours could be reasonable,[8] the treatment window of 6–24 hours after the onset for patients with BAO might be beneficial in recent trials.[5–7] Based on these real-world data, the time from IVT to groin puncture in our bridging group was significantly longer than those with an anterior-circulation LVO. However, we found that patients in the bridging group had significantly better outcomes than DEVT if IVT was given <4.5 hours, even though EVT was initiated up to 24 hours after onset. The benefit of IVT first appeared to persist, without increasing the risk of haemorrhage, even if EVT was delivered at a later time, up to 24 hours after onset. This may have provided some evidence that in patients with acute BAO and those who need to be transferred to a comprehensive stroke centre, bridging with IVT first should be considered.[15] Nevertheless, the earlier the EVT is initiated, the more effective the therapy will be and with better safety profile.[16 17] In our subgroup analysis, we also found that patients with shorter onset to door time (≤3 hours), fast groin puncture time (≤6 hours) and faster recanalisation time (≤12 hours) had a better outcome after bridging treatment.

Potential advantages of bridging therapy include early thrombus fragmentation, microvascular reperfusion and enhanced recanalisation.[18–20] Subgroup analysis of the ESCAPE trial (Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times Trial) indicated that pretreatment with IVT reduced approximately by two-thirds the likelihood of infarct in a new previously unaffected territory complicating DEVT, whereas infarct in a new previously unaffected territory was in turn associated with substantial reduction in the odds of functional improvement quantified using the shift in mRS score.[21] Posterior-circulation occlusions are significantly associated with distal emboli in the same and previously unaffected territories during thrombectomy. This may be partially ameliorated with bridging tissue plasminogen activator and result in better outcomes.[22 23] The bridging approach has possible benefits in certain individual cases (eg, patients within the very early time window and with short dense clot, distal thrombus location, high residual flow permeability, good collaterals, or drip and ship thrombolysis), but they seem to be low as revealed by a previous study.[24] However, based on the results of the meta-analysis, the overall reperfusion status after EVT in BAO was lower than in anterior-circulation LVO. Early reocclusion and EVT failure were more common in BAO, causing a lower reperfusion rate.[1] Besides, 80.97% of the stroke cases in BAO were from atherosclerosis, a higher proportion compared with that in the anterior-circulation LVO. Therefore, theoretically, BAO might benefit more from IVT first.

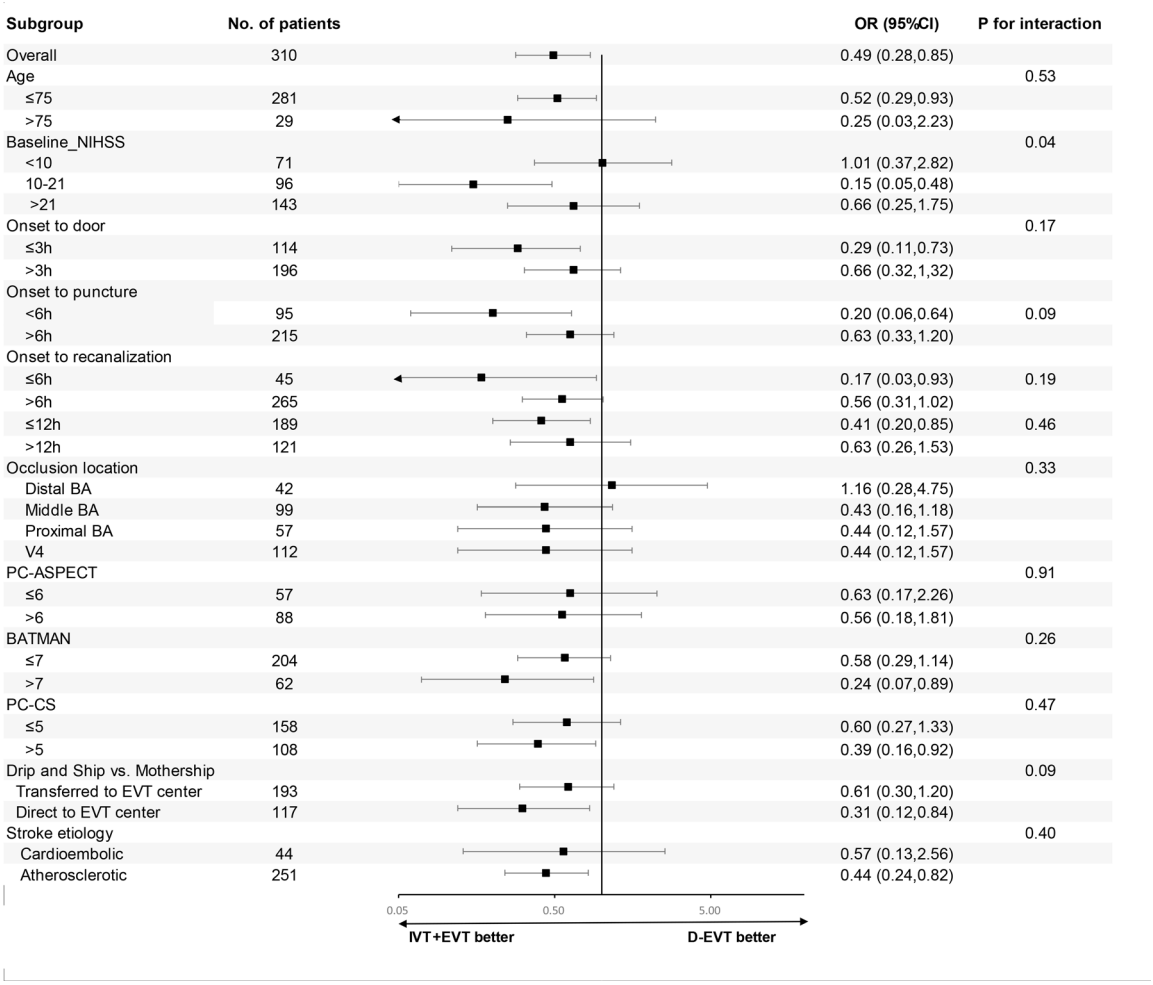

Figure 3 Subgroup analysis. This forest plot shows the difference in the primary clinical outcome across all subgroups. The OR was calculated by using logistic regression, taking the following variables into account: age, baseline NIHSS score, onset to door time, onset to puncture time, onset to recanalisation time, occlusion location, collateral status and aetiology of stroke. The thresholds for baseline age were chosen at the median. P value for comparison between patients treated with DEVT and patients treated with bridging treatment. BA, basilar artery; BATMAN, Basilar Artery on Computed Tomography Angiography; DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECT, Posterior Circulation Alberta Stroke Program Early Computed Tomography Score; PC-CS, Posterior Circulation Collateral Score.

Table 4 Outcomes of RESCUE-RE and the EVT arms of pivotal EVT studies on BAO

Study	Arm (n)	IVT	mTICI ≥2b	mRS 0–2	Death	sICH
RESCUE-RE 2021						
DEVT arm	241	0	181 (75.1)	63 (26.1)	63 (26.1)	21 (8.7)
IVT+EVT arm	69	69 (100)	47 (68.1)	29 (42.0)	13 (18.8)	5 (7.3)
BEST 2019 (EVT arm)	65	18 (27.7)	45 (71.0)	22 (33.0)	22 (33.0)	5 (8.0)
BASICS 2021 (EVT arm)	154	121 (78.6)	63/88* (72.0)	54 (35.1)	59 (38.3)	7 (4.5)
BASILAR 2020 (EVT arm)	647	119 (18.4)	522 (80.7)	177 (27.4)	299 (46.2)	45 (7.1)

*88 of 154 patients enrolled in the EVT arm of BASICS were analysed.
BAO, acute basilar artery occlusion; BASICS, Basilar Artery International Cooperation Study; BASILAR, EVT for Acute Basilar Artery Occlusion Study; BEST, Endovascular Treatment versus Standard Medical Treatment for Vertebrobasilar Artery Occlusion trial; DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction Score; RESCUE-RE, Registration Study for Critical Care of Acute Ischemic Stroke After Recanalization; sICH, symptomatic intracranial haemorrhage.

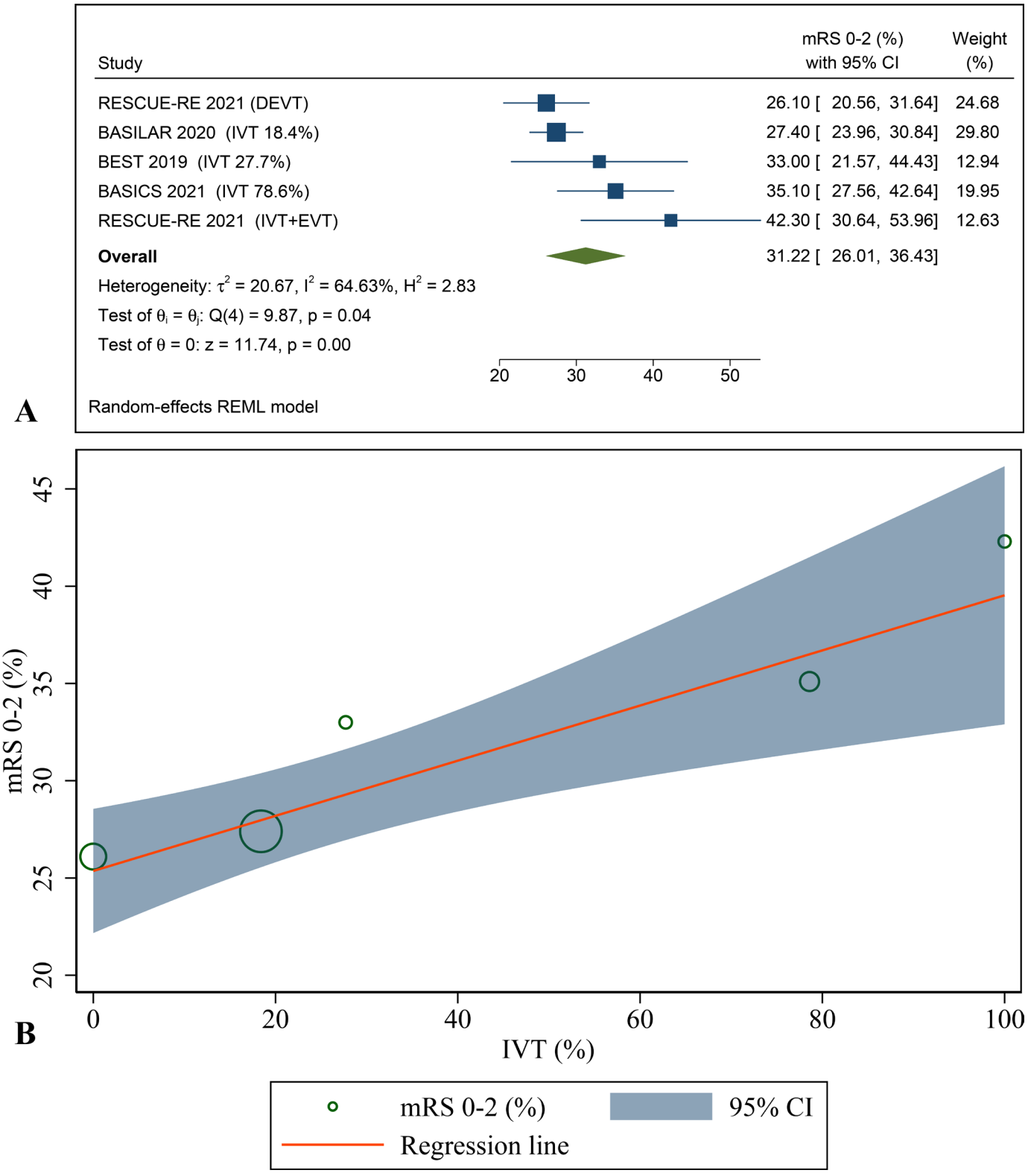

Figure 4 (A) Meta-analysis (functional independence, mRS 0–2 at 90 days (%)) of each arm of RESCUE-RE and the EVT arms of pivotal EVT trials on BAO using the restricted maximum likelihood random-effects method. (B) Meta-analysis regression of IVT (%) in each arm of RESCUE-RE and the EVT arms of pivotal EVT trials on BAO on the functional independence using restricted maximum likelihood random-effects method. BAO, basilar artery occlusion; BASICS, Basilar Artery International Cooperation Study; BASILAR, EVT for Acute Basilar Artery Occlusion Study; BEST, Endovascular Treatment versus Standard Medical Treatment for Vertebrobasilar Artery Occlusion trial; DEVT, direct endovascular treatment; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; RESCUE-RE, Registration Study for Critical Care of Acute Ischemic Stroke After Recanalization; REML, restricted maximum-likelihood random-effects.

Several studies reported that IVT was associated with increased risk of haemorrhagic transformation, delayed initiation of the EVT procedure, adverse thrombus migration and fragmentation, resulting in thrombi that were out of reach for mechanical thrombectomy.[25–27] IVT prior to EVT seemed useless for patients with long clots, low clot burden scores, proximal occlusions, long onset to treatment time or with calcific emboli.[28] However, in the current study, the 90-day mortality and sICH were not statistically different between the two groups, similar as in treating anterior-circulation LVO. Furthermore, no difference was found in problems with workflow between the two groups. Patients with BAO are often found with a higher percentage of intracranial stenoses and tortuous vessels in the vertebrobasilar artery system,[29] which would increase the difficulty of EVT. This potential difficulty in EVT operation was confirmed by the current study, as the DEVT group had more patients who needed ≥3 passes with stent retriever.[30]

While the results of the current study may not be sufficient to affirm or negate the value of IVT prior to EVT for anterior-circulation LVO, it is important to acknowledge that there are many individual variables in the decision-making process that may not be captured in clinical trials.[28] Recently, several studies have reported prognostic factors for clinical outcome in patients with acute BAO after mechanical thrombectomy.[13 31 32] Although there are some differences in the cut-off value, BASICS reported an initial modest NIHSS score before EVT as a possible predictor of good outcome.[5] Our study indicated that IVT+EVT might provide a more favourable outcome for patients with BAO with an NIHSS score between 10 and 21. In addition, in younger patients (≤75 years), good collateral status (BATMAN >7 or PC-CS >5) and direct to EVT centre, IVT+EVT could provide a better outcome compared with DEVT. However, further validation through large and randomised trials is needed since the data were from a subgroup analysis.

On the site of basilar occlusion, previous studies[13 33] identified that distal BAO was a possible favourable predictor of outcome due to probably better collaterals. Distal BAO may present with fewer initial neurological symptoms, a shorter clot burden and a higher probability of successful recanalisation. The subgroup analysis in the current study showed that bridging treatment might not have any advantage in patients with distal BAO compared with DEVT.

The current study has several limitations. First, this study was an observational study. How treating clinicians select a specific treatment is a complex issue in the real world. Multivariable analyses cannot adjust completely for systematic differences between treatment groups without a randomised trial. Second, there was potential selection bias as the treatment group was stratified based on the selective clinical criteria (IVT contraindications, for instance). About 30% of patients in the DEVT group had contraindications to IVT, which may carry a poor prognosis.[34] Third, more patients received DEVT, a potential of lack of equipoise among participating centres.[7] Fourth, the time delay between hospital arrival and arterial puncture for EVT was longer than that in RCTs and guidelines, which might influence the results. In addition, the percentage of atherosclerosis was higher than reported in other BAO studies, which may reflect the Asian Intracranial atherosclerotic disease (ICAD) preponderance, but reduces the generalisability of this study. Lastly, the study enrolled patients with BAO who were chosen to receive EVT based on limited level of evidence and thus the findings should be treated with caution and be further confirmed by well-designed RCTs. There were also several limitations to the meta-analysis, such as substantial heterogeneity in the overall analysis, selection bias and other possible bias and confounding bias, which might impact the results. An ongoing RCT (NCT03494920) enrolling both patients with anterior-circulation and posterior-circulation LVO should be able to provide conclusive results.

In conclusion, a significant difference in terms of functional outcome was observed in patients with BAO-AIS treated within 24 hours of onset with either bridging therapy or DEVT. The data showed bridging therapy might bring better functional outcomes at 90 days than those treated with EVT alone after adjusting for potential confounders, notably in patients with an initial modest NIHSS score (10–21) at onset. IVT first may provide additional benefits. Furthermore, the regression meta-analysis revealed a potential positive correlation between IVT first and functional independence. Overall, the results of the current study indicated that bridging therapy may be potentially favourable for BAO and in improving functional outcomes. More RCTs are needed to confirm these findings.

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REFERENCES

1 Mattle HP, Arnold M, Lindsberg PJ, *et al*. Basilar artery occlusion. *Lancet Neurol* 2011;10:1002–14.
2 Schonewille WJ, Wijman CAC, Michel P, *et al*. Treatment and outcomes of acute basilar artery occlusion in the basilar artery international cooperation study (BASICS): a prospective registry study. *Lancet Neurol* 2009;8:724–30.
3 Powers WJ, Derdeyn CP, Biller J, *et al*. 2015 American heart Association/American stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2015;46:3020–35.
4 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
5 Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, *et al*. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med* 2021;384:1910–20.
6 Liu X, Dai Q, Ye R, *et al*. Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (best): an open-label, randomised controlled trial. *Lancet Neurol* 2020;19:115–22.
7 Writing Group for the BASILAR Group, Zi W, Qiu Z, *et al*. Assessment of endovascular treatment for acute basilar artery occlusion via a nationwide prospective registry. *JAMA Neurol* 2020;77:561–73.
8 Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2018;49:e46–110.
9 Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
10 Zi W, Qiu Z, Li F, *et al*. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234–43.
11 Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12:1500–24.
12 Wei Y, Pu Y, Pan Y, *et al*. Cortical microinfarcts associated with worse outcomes in patients with acute ischemic stroke receiving endovascular treatment. *Stroke* 2020;51:2742–51.
13 Kwak HS, Park JS. Mechanical thrombectomy in basilar artery occlusion: clinical outcomes related to posterior circulation collateral score. *Stroke* 2020;51:2045–50.
14 Larrue V, von Kummer R R, Müller A, *et al*. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian acute stroke study (ECASS II). *Stroke* 2001;32:438–41.
15 Fassbender K, Walter S, Grunwald IQ, *et al*. Prehospital stroke management in the thrombectomy era. *Lancet Neurol* 2020;19:601–10.
16 Ravindren J, Aguilar Pérez M, Hellstern V, *et al*. Predictors of outcome after endovascular thrombectomy in acute basilar artery occlusion and the 6hr time window to recanalization. *Front Neurol* 2019;10:923.
17 Lindsberg PJ, Pekkola J, Strbian D, *et al*. Time window for recanalization in basilar artery occlusion: Speculative synthesis. *Neurology* 2015;85:1806–15.
18 Desilles J-P, Loyau S, Syvannarath V, *et al*. Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. *Stroke* 2015;46:3241–8.
19 Mueller L, Pult F, Meisterernst J, *et al*. Impact of intravenous thrombolysis on recanalization rates in patients with stroke treated with bridging therapy. *Eur J Neurol* 2017;24:1016–21.
20 Fjetland L, Kurz KD, Roy S, *et al*. Evaluation of the recombinant tissue plasminogen activator pretreatment in acute stroke patients with large vessel occlusions treated with the direct bridging approach. is it worth the effort? *Eur J Neurol* 2015;22:322–7.
21 Ganesh A, Al-Ajlan FS, Sabiq F, *et al*. Infarct in a new Territory after treatment administration in the escape randomized controlled trial (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times). *Stroke* 2016;47:2993–8.
22 Meyer L, Stracke CP, Jungi N, *et al*. Thrombectomy for primary distal posterior cerebral artery occlusion stroke: the TOPMOST study. *JAMA Neurol* 2021;78:434–44.
23 Yeo LLL, Holmberg A, Mpotsaris A, *et al*. Posterior Circulation Occlusions May Be Associated with Distal Emboli During Thrombectomy : Factors for Distal Embolization and a Review of the Literature. *Clin Neuroradiol* 2019;29:425–33.
24 Fischer U, Kaesmacher J, Molina CA, *et al*. Primary thrombectomy in tPA (tissue-type plasminogen activator) eligible stroke patients with proximal intracranial occlusions. *Stroke* 2018;49:265–9.
25 Chandra RV, Leslie-Mazwi TM, Mehta BP, *et al*. Does the use of IV tPA in the current era of rapid and predictable recanalization by mechanical embolectomy represent good value? *J Neurointerv Surg* 2016;8:443–6.
26 Fischer U, Kaesmacher J, Mendes Pereira V, *et al*. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke: a topical review. *Stroke* 2017;48:2912–8.
27 Ren Y, Churilov L, Mitchell P, *et al*. Clot migration is associated with intravenous thrombolysis in the setting of acute ischemic stroke. *Stroke* 2018;49:3060–2.
28 Nogueira RG, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? *Stroke* 2020;51:3182–6.
29 Keselman B, Gdovinová Z, Jatuzis D, *et al*. Safety and outcomes of intravenous thrombolysis in posterior versus anterior circulation stroke: results from the safe implementation of treatments in stroke Registry and meta-analysis. *Stroke* 2020;51:876–82.
30 Maros ME, Brekenfeld C, Broocks G, *et al*. Number of retrieval attempts rather than procedure time is associated with risk of symptomatic intracranial hemorrhage. *Stroke* 2021;52:1580–8.
31 Singer OC, Berkefeld J, Nolte CH, *et al*. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. *Ann Neurol* 2015;77:415–24.
32 Mokin M, Sonig A, Sivakanthan S, *et al*. Clinical and procedural predictors of outcomes from the endovascular treatment of posterior circulation strokes. *Stroke* 2016;47:782–8.
33 Puetz V, Dzialowski I, Hill MD, *et al*. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. *Int J Stroke* 2008;3:230–6.
34 Linfante I, Starosciak AK, Walker GR, *et al*. Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. *J Neurointerv Surg* 2016;8:224–9.

Table S1. Characteristics of the studies included in the meta-analysis

Variable	BASICS 2021	BEST 2019	BASILAR 2020	RESCUE-RE (BAO) 2021
Start time, y	2011	2015	2018	2018
Publication time, y	2021	2019	2020	NA
Location	23 centers in 7 countries	28 centers in China	47 centers in China	18 centers in China
Study type	mRCT	mRCT	Cohort study	Cohort study
Participant				
Image criteria	BAO on CTA/MRA	BAO on CTA/MRA/DSA	BAO on CTA/MRA/DSA	BAO on CTA/MRA/DSA
NIHSS	≥10 in proposal	NA	NA	NA
Time (h)	<6h	<8h	<24h	<24h
Number of BAO patients in EVT groups	154/300	65/131	647/829	310/1701
IVT, n (%)	121 (78.6)	18 (27.7)	119 (18.4)	69 (22.3)
Age, Mean± SD, y	66.8±13.1	62 (IQR 50−74)	64 (IQR 56-73)	61.4±10.9
Male, n (%)	100 (64.9)	48 (72.7)	483 (74.7)	240 (77.4)
B-NIHSS, Median (IQR)	21	32 (18–38)	27 (17-33)	21 (11-27)
OTP, Median (IQR), min	264 (198–372)	246 (139-360)	328 (220-493)	485 (333-835)
Randomization	Randomized 1:1, PROBE	Randomized 1:1, PROBE	Nonrandomized	Nonrandomized
Intervention/ Exposome	EVT	EVT	EVT	DEVT
Control	SMT	SMT	SMT	IVT+EVT
ITT	Yes	Yes	NA	NA
Primary outcome	mRS 0-3	mRS 0-3	mRS score	mRS 0-2
Follow-up	90 days	90 days	90 days	90 days

Abbreviations: RESCUE-RE, a registration study for critical care of acute ischemic stroke after recanalization; BEST, acute basilar artery occlusion: endovascular interventions versus standard medical treatment trial; BASICS, basilar artery international cooperation study; BASILAR, the EVT for acute basilar artery occlusion study. mRCT, multicenter Randomized Controlled Trial; BAO, basilar artery occlusion; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, interquartile range; mRS, modified Rankin Scale; OTP, onset to puncture; IVT, intravenous thrombolysis; EVT, endovascular treatment; DEVT, direct endovascular treatment; SMT, standard medical therapy; ITT, intention-to-treat analysis.

Supplementary of meta-analysis

Method supplementary

Search strategy:

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement were followed in this meta-analysis. PubMed, EMBASE, and Cochrane library were searched for English peer-reviewed publications that were published from Jan 1, 2015 to Jun 30, 2021. Randomized trials and high-quality cohort studies that compared IVT with EVT for the BAO patients were identified. Search strategy included the combination of terms, such as "cerebrovascular disorder", "basilar artery occlusion", "stroke", "thrombolysis", "thrombectomy", "vertebral", "posterior circulation", "aspiration", "stentretriever", "ischemic", as either keywords or MeSH terms. Related reviews, clinical trial databases, and the reference lists of all retrieved articles were also searched manually to identify relevant studies.

Search strategy in PubMed database for example:

("Stroke" [Mesh] OR Cerebrovascular event[Title/Abstract] OR Stroke[Title/Abstract] OR CVA[Title/Abstract] OR cerebrovascular accident[Title/Abstract] OR brain vascular accident[Title/Abstract] OR brain isch[Title/Abstract] OR brain infarc*[Title/Abstract] OR cerebral infarc*[Title/Abstract] OR cerebral isch* OR cerebral vessel occlusion[Title/Abstract] OR large vessel occlusion[Title/Abstract] OR intracranial*

isch[Title/Abstract] OR intracranial infarction[Title/Abstract] OR intracranial vessel occlusion [Title/Abstract] OR brain vessel occlusion [Title/Abstract]) AND (Thrombectomy [Mesh] OR Thrombectomy[Title/Abstract] OR thrombectom*[Title/Abstract] OR mechanical[Title/Abstract] OR endovascular[Title/Abstract] OR embolectomy[Title/Abstract] OR intracranial intervention[Title/Abstract] OR Stent-retriever[Title/Abstract] OR stentretriever[Title/Abstract] OR preset[Title/Abstract] OR solitaire[Title/Abstract] OR trevo[Title/Abstract] OR catch[Title/Abstract] OR aspiration[Title/Abstract] AND (Tissue Plasminogen Activator [Mesh] OR bridging*[Title/Abstract] OR thrombolysis[Title/Abstract] OR rtPA[Title/Abstract] OR tpA[Title/Abstract] OR rt PA[Title/Abstract] OR alteplase[Title/Abstract] OR bridging-therapy[Title/Abstract]OR plasminogen activator[Title/Abstract] or recombinantplasminogen[Title/Abstract] OR plasminogen-activator [Title/Abstract]) AND (direct[Title/Abstract] OR combined[Title/Abstract] OR with[Title/Abstract] OR alone[Title/Abstract] OR combination[Title/Abstract] OR preceding[Title/Abstract] OR preinterventional[Title/Abstract] OR prior [Title/Abstract] OR before [Title/Abstract] OR previous [Title/Abstract] OR concomitant [Title/Abstract] or stand-alone [Title/Abstract] or together [Title/Abstract] or following [Title/abstract] or followed [Title/abstract]) or eligible [Title/abstract] or contraindication [Title/abstract] or ineligible [Title/abstract] or preproced*[Title/abstract] or preinterv*[Title/abstract] or prethrom*[Title/abstract] or pre-proced*[Title/abstract] or preinter*[Title/abstract] or pre-throm*[Title/abstract]) AND (basilar artery [MeSH Terms] OR posterior [Title/abstract] OR posteriors [Title/abstract] OR blood[Title/abstract] OR

circulation[Title/abstract] OR blood circulation[Title/abstract] OR circulation[Title/abstract] OR circulations[Title/abstract] OR circulate[Title/abstract] OR circulated[Title/abstract] OR circulates[Title/abstract] OR circulating[Title/abstract] OR artery[Title/abstract] OR basilar artery[Title/abstract] OR occlusion [Title/abstract] OR occlused [Title/abstract] OR occlusions[Title/abstract] OR occlusive[Title/abstract] OR occlusives[Title/abstract] OR basilar[Title/abstract] AND artery[Title/abstract] OR basilar artery[Title/abstract] AND artery[Title/abstract] OR basilar artery[Title/abstract]

Selection criteria:

According to the objective of this analysis, only randomized trials and high-quality cohort studies plus the current cohort study that reported reporting the clinical efficacy, safety of EVT and percentage of IVT used in EVT group among adult (≥18) patients with acute basilar artery occlusion. We limited the studies to English language and excluded case reports, small size cohort (< 100), conference proceedings, and reviews.

Outcomes Measure:

The outcome was good functional outcome at 3 months. Good functional outcome after 3 months was defined as a modified Rankin score (mRS) of 0-2 at 3 months after stroke onset.

Data extraction

Two physicians independently extracted data from identified publications based on the inclusion criteria. Disagreements were resolved through the discussion among all authors until a consensus was reached. Data on the total number of patients treated with EVT, onset-to-EVT time, percentage of IVT used before EVT and duration of follow-up, were extracted from publications. The occurrence of the following events was extracted for individual trials and analyzed for the EVT group: total patients, treated with IVT, with a mRS of 0-2, and deceased patients at 90 days (IVT+EVT group and DEVT group of RESCUE-RE were analyzed separately). Characteristic data were also retrieved. Between-study heterogeneities were evaluated by the I^2 statistic and the Cochrane Q (χ^2) statistic, with a P value of 0.05 set to be significant for heterogeneity.

Result supplementary

Heterogeneity, risk of bias and quality assessment

There was significant heterogeneity across the four studies (five EVT groups, I^2=64.63%, p<0.01), but no significant heterogeneity was found in subgroups on onset-to-EVT time and There was no statistical difference of functional independence between the two subgroups (Figure S1). There was also no significant publication bias detected with the examination of funnel plots for the outcome of functional independence (Figure S2) or

with Egger's regression test (P=0.095). The GRADE system assesses evidence quality with four levels: high, moderate, low, or very low. The initial grading would be decreased if there were study limitations, inconsistencies, imprecision, indirectness, or publication bias (Table S2).

Table S2. Quality evaluation of the 4 included studies according to the GRADE scale

Study	Risk of bias	Indirectness	Imprecision	Publication bias	Large effect	Plausible residual confounding	Total	Quality of evidence
RESCUE-RE 2021	-1	0	0	0	0	0	1	Very low
BEST 2019	0	-1	0	0	0	0	3	Moderate
BASICS 2021	0	-1	0	0	0	0	3	Moderate
BASILAR 2020	-1	-1	0	0	0	0	0	Very low

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IVT, intravenous thrombolysis; EVT, endovascular treatment; RESCUE-RE, registration study for critical care of acute ischemic stroke after recanalization registry; BEST, endovascular interventions versus standard medical treatment trial; BASICS, basilar artery international cooperation study; BASILAR, the EVT for acute basilar artery occlusion study.

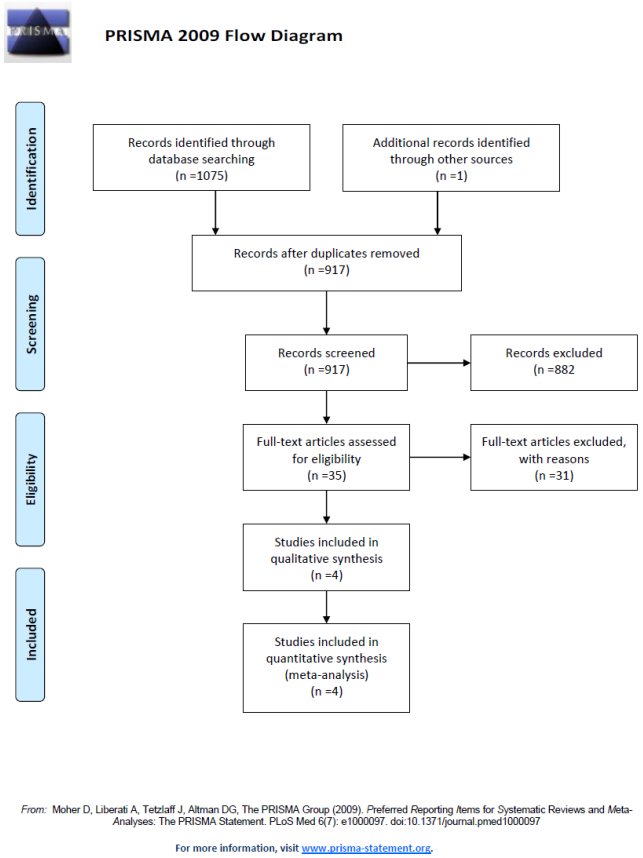

Figure S1. Flow diagram

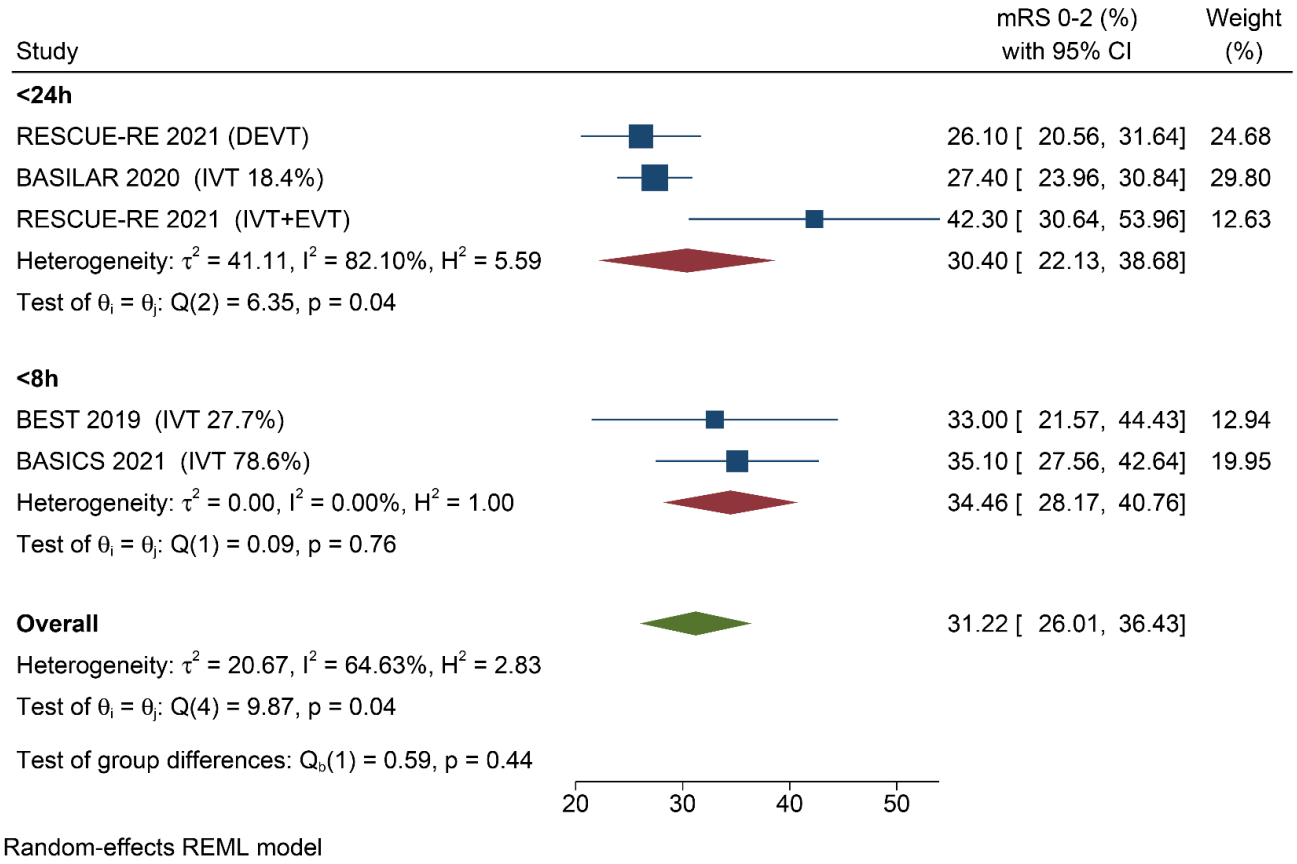

Figure S2. Stratified analysis by onset-to-EVT time of meta-analysis (functional independence, mRS 0-2 at 90d [%]) of each arm of RESCUE-RE and EVT arms of pivotal EVT trials on BAO with restricted maximum-likelihood random-effects method.

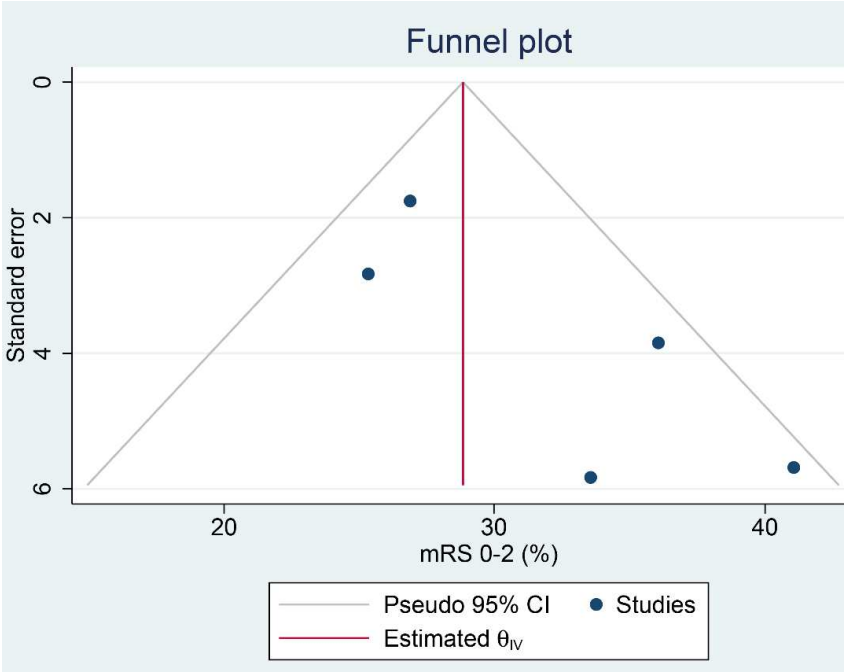

Figure S3. Risk of publication bias: funnel plot for the outcome of functional independence.