Systematic review

Endovascular treatment for large-core ischaemic stroke: a meta-analysis of randomised controlled clinical trials

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ABSTRACT

Background and purpose Current guidelines recommend endovascular treatment (EVT) for acute ischaemic stroke (AIS), due to large-vessel occlusion and an Alberta Stroke Program Early CT Score (ASPECTS) of ≥6. High-quality evidence resulting from randomised controlled clinical trials (RCTs) regarding EVT among large-core AIS has recently become available, justifying an updated meta-analysis aiming to evaluate efficacy and safety of EVT in this clinical setting.

Methods We conducted a systematic review and meta-analysis including all available RCTs that compared EVT in addition to best medical treatment (BMT) versus BMT alone for large-core AIS (defined by ASPECTS 2–5 or volumetric methods). The primary outcome was reduced disability at 3 months (≥1-point reduction across all Modified Rankin Scale (mRS) grades). Secondary outcomes included independent ambulation at 3 months (mRS score 0–3), good functional outcome at 3 months (mRS score 0–2), excellent functional outcome at 3 months (mRS score 0–1), symptomatic intracranial haemorrhage (sICH) and any intracranial haemorrhage (ICH) and mortality at 3 months. The random-effects model was used.

Results Four RCTs were included comprising a total of 662 patients treated with EVT vs 649 patients treated with BMT. Compared with BMT, EVT was significantly associated with reduced disability (common OR 1.70, 95% CI 1.39 to 2.07; I^2=0%), independent ambulation (risk ratio (RR) 1.69, 95% CI 1.33 to 2.14; I^2=39%) and good functional outcome (RR 2.33, 95% CI 1.76 to 3.10; I^2=0%), but not with excellent functional outcome (RR 1.46, 95% CI 0.91 to 2.33; I^2=39%) at 3 months. Although rates of sICH (RR 1.98, 95% CI 1.07 to 3.68; I^2=0%) and any ICH (RR 2.13, 95% CI 1.70 to 2.66; I^2=37%) were higher in the EVT group, 3-month mortality (RR 0.98, 95% CI 0.83 to 1.15; I^2=0%) did not differ between the two groups.

Conclusion EVT appears to be effective and safe and may be considered for the treatment of large-core AIS, as assessed by ASPECTS of 2–5 or volumetric methods.

PROSPERO registration number CRD42022334417.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Endovascular treatment (EVT) for acute ischemic stroke (AIS) attributed to large vessel occlusion of the anterior circulation is indicated according to international recommendations for patients presenting within 6 hours from stroke onset, with a National-Institutes-of-Health-Stroke-Scale (NIHSS) score 6 or more, and an Alberta-Stroke-Program-Early-CT-Score (ASPECTS) ≥6. A recent systematic review and meta-analysis has shown that EVT was associated with a higher likelihood of achieving mRS-scores of 0-3 when compared to best medical treatment (BMT). Yet, this review was limited by the inclusion of mostly observational data.

WHAT THIS STUDY ADDS

⇒ This is the first systematic review and meta-analysis of the all available RCTs so far, showing that EVT plus BMT in the treatment of patients with large-core AIS is associated with a higher likelihood of reduced disability, independent ambulation and good functional outcome at 3 months compared to BMT alone. Excellent functional outcome did not significantly differ between the two groups. Although symptomatic intracranial hemorrhage and any intracranial hemorrhage were more common in the EVT group, 3-month mortality did not differ between the groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current meta-analysis provides promising results that EVT is safe and effective and may be considered in everyday clinical practice in patients with large-core AIS, as assessed by an ASPECTS of 2-5 or volumetric methods.

BACKGROUND

Endovascular treatment (EVT) for acute ischaemic stroke (AIS) attributed to large-vessel occlusion of the anterior circulation has been indicated for patients presenting within 6 hours from stroke onset, with a National Institutes of Health Stroke Scale score of 6 or more and an Alberta Stroke Program Early CT Score (ASPECTS) of ≥6.[1,2] Yet, previous exclusion criteria for EVT are actively being challenged, and the current indications have expanded. The first barrier that was surpassed was the time-window restriction that has now been increased to

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24 hours for patients fulfilling advanced neuroimaging criteria.[1] Another challenge is the treatment of patients presenting with large-core AIS based on measurement of ischaemic-core volumes or ASPECTS of <6. A recent systematic review and meta-analysis of observational studies and randomised controlled clinical trials (RCTs) showed that almost 40% of patients with large-core AIS who underwent EVT had a 3-month Modified Rankin Scale (mRS) score of 0–3. In addition, EVT was associated with a higher likelihood of achieving mRS scores of 0–3 when compared with best medical treatment (BMT).[3] Yet, this review was limited by the inclusion of mostly observational data.

The results of three RCTs investigating the efficacy and safety of EVT among patients with large-core AIS have been recently presented: the Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core (ANGEL-ASPECT),[4] the Randomised Controlled Trial to Optimize Patient Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2)[5] and the Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (TESLA)[6 7] studies. These trials complemented the previously published results of another RCT, the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large Ischemic core Trial (RESCUE-Japan LIMIT).[8] Given these recent, high-quality, randomised data, we performed a systematic review and study-level meta-analysis based on RCT data only, with the aim to evaluate the efficacy and safety of EVT in patients with large-core AIS.

METHODS

The prespecified protocol of the present systematic review and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews (registration ID: CRD42022334417) and is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] The methodology used was similar to our previous work.[3] Briefly, a systematic literature search was conducted through MEDLINE and Scopus databases to identify RCTs reporting on patients with large-core AIS (defined by ASPECTS 2–5 or volumetric methods) treated with EVT compared with BMT. We additionally searched reference lists of published articles and international conference abstracts manually to ensure the comprehensiveness of bibliography. Last literature search was conducted on 30 May 2023. The primary outcome was reduced disability at 3 months (≥1-point reduction across all mRS grades). Secondary outcomes included independent ambulation at 3 months (mRS score 0–3), good functional outcome at 3 months (mRS score 0–2), excellent functional outcome at 3 months (mRS score 0–1), symptomatic intracranial haemorrhage (sICH; as defined by each RCT), any intracranial haemorrhage (ICH) and mortality at 3 months. Data were extracted by scrutinising the peer-reviewed publications of the included RCTs and their online supplemental materials.

STATISTICAL ANALYSIS

For the primary outcome, the unadjusted common OR (cOR) was calculated using generic inverse variance meta-analysis. For the pairwise meta-analysis, we calculated for each dichotomous outcome of interest the corresponding unadjusted risk ratios (RRs) with 95% CIs for the comparison of outcome events among patients undergoing EVT versus controls. Comparison of the baseline characteristics to assess the balance between the two arms was performed using OR for dichotomous variables and the mean difference or the difference of medians for continuous variables, as applicable. The random-effects model of meta-analysis (DerSimonian and Laird) was used to calculate the pooled estimates.[10] All statistical analyses were performed using the R software V.3.5.0 (packages: meta and metamedian).[11]

Data availability statement

All data generated and analysed are included in this report and its online supplemental information files.

RESULTS

Four RCTs were included (online supplemental figure 1 and table 1), comprising a total of 662 patients treated with EVT vs 649 patients treated with BMT alone, with no significant baseline differences between the two groups (online supplemental figures 2–8). The characteristics of the included studies are presented in table 1. All RCTs presented moderate risk of bias (online supplemental figures 9–10).

Treatment with EVT was significantly associated with reduced disability at 3 months (cOR 1.70, 95% CI 1.39 to 2.07; $I^2=0\%$; figure 1A) compared with BMT alone. In a sensitivity analysis, using the generalised OR as reported in two RCTs,[4 5] we found that the overall result did not differ (online supplemental figure 11). In a subgroup analysis stratifying for onset-to-randomisation time (<6 hours vs ≥6 hours), no difference was disclosed between the two subgroups (p value for subgroup differences=0.57; online supplemental figure 12). Patients undergoing EVT had an increased likelihood of achieving independent ambulation (RR 1.69, 95% CI 1.33 to 2.14; $I^2=39\%$; figure 1B) and good functional outcome (RR 2.33, 95% CI 1.76 to 3.10; $I^2=0\%$; figure 1C) at 3 months compared with BMT alone. Excellent functional outcome at 3 months did not differ between the two groups (RR 1.46, 95% CI 0.91 to 2.33; $I^2=18\%$; figure 1D).

With regard to the safety outcomes, there was a higher likelihood of sICH (RR 1.98, 95% CI 1.07 to 3.68; $I^2=0\%$; online supplemental figure 13A) and any ICH (RR:2.13; 95% CI:1.70 to 2.66; $I^2=37\%$; online supplemental figure 13B) among the patients treated with EVT compared with patients receiving BMT. Due to the fact that ICH was reported within 24 hours post treatment in SELECT2[5] and in TESLA[6 7] trials (in contrast to the other two RCTs that reported this outcome up to 48 hours post treatment),[4 8] sensitivity analyses were performed by excluding SELECT2 and TESLA, yielding similar results for both sICH and any ICH (online supplemental figures 14–15). Since different definitions of sICH were used by the included RCTs, a subgroup analysis was conducted, stratifying for the sICH definition used, confirming similar results between the two subgroups (p value for subgroup differences=0.69; online supplemental figure 16). Finally, 3-month mortality was similar between EVT and BMT groups (RR 0.98, 95% CI 0.83 to 1.15; $I^2=0\%$; online supplemental figure 13C).

Pooled rates of each outcome separately for the EVT-treated and the BMT-treated patients are presented in online supplemental table 2. We also conducted a sensitivity analysis after excluding the ANGEL-ASPECT trial,[4] which contributed substantially to the heterogeneity of the reported outcomes per treatment arm across the three RCTs, and obtained similar results (online supplemental figures 17–23).

DISCUSSION

The present meta-analysis of available RCT data has shown that EVT plus BMT in the treatment of patients with large-core AIS is associated with a higher likelihood of reduced disability, independent ambulation and good functional outcome at 3 months

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Study	Recruiting centres	Period of enrolment	Inclusion criteria					Imaging used to evaluate ASPECTS	Included patients (N)	EVT	BMT
			Years of age	NIHSS score	Prestroke mRS score	Stroke onset	Large core				
ANGEL-ASPECT[4]	China	October 2020–May 2022	18–80	6–30	0–1	Within 24 hours	ASPECTS 3–5 OR an ischaemic-core volume of 70 to 100 ml.	Non-contrast CT	456	231	225
RESCUE-Japan LIMIT[8]	Japan	November 2018–September 2021	>18, no upper age limit	≥6, no upper limit	0–1	Within 6 hours or within 24 hours and no FLAIR early changes	ASPECTS 3–5	Non-contrast CT or diffusion-weighted MRI	203	101	102
SELECT2[5]	International	September 2019–September 2022	18–85	≥6, no upper limit	0–1	Within 24 hours	ASPECTS 3–5 or an ischaemic-core volume of at least 50 mL (no upper limit for volume of ischaemic core)	Non-contrast CT	352	178	174
TESLA[6 7]	USA	July 2019–October 2022	18–85	≥6, no upper limit	0–1	Within 24 hours	ASPECTS 2–5	Non-contrast CT	300	152	148

ANGEL-ASPECT, Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; ASPECTS, Alberta Stroke Program Early CT Score; BMT, Best Medical Treatment; EVT, Endovascular Treatment; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RESCUE Japan-LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large Ischemic core Trial; SELECT2, Randomised Controlled Trial to Optimize Patient Selection for Endovascular Treatment in Acute Ischemic Stroke; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke.

compared with BMT alone. Excellent functional outcome did not significantly differ between the two groups. Moreover, although sICH and any ICH were more common in the EVT group, 3-month mortality did not differ between the groups.

These findings support the results of previous meta-analyses showing that EVT is associated with better functional outcomes compared with BMT in patients with large-core AIS, without raising any serious safety concerns.[3 12–17] These meta-analyses, however, were mostly based on observational data, presenting moderate-to-serious risk of bias, while a subset of them included patients either with higher-than-required ASPECTS (ie, 6, for which there is a clear indication for intervention) or very low ASPECTS (ie, including 0–4 and excluding 5), potentially diluting the reported findings. Our current work provides exclusively the synthesis of all completed RCTs, which included patients with AIS with occlusion of the internal carotid artery and/or M1 segment of the middle cerebral artery and an ASPECTS of 2–5 or, additionally, in the cases of ANGEL-ASPECT[4] and SELECT2,[8] patients with a large ischaemic core, as assessed be volumetric methods (between 70–100 and >50 mL, respectively). Treatment had to be administered within 24 hours from stroke onset, provided that there were no MRI-fluid attenuated inversion recovery (FLAIR) early changes in the case of RESCUE-Japan LIMIT.[8]

Another important point that should be considered is the fact that patients within 6–24 hours since stroke onset were also amenable for inclusion and presented similar outcomes to those treated within the first 6 hours. In this setting, not one but two of the previously imposed restrictions (time window and large core) had been successfully surpassed, resonantly proving the efficacy of EVT in patients' populations that would have otherwise been excluded. Despite these compelling results, it should be stated that more RCTs are still ongoing (eg, TENSION/NCT03094715), and their results are awaited with

the optimism of robustly establishing the indication of EVT in this AIS subgroup.[18]

The main strength of our study is the exclusive inclusion of all available RCTs that have been completed and presented to date. Yet, there are certain limitations that need to be acknowledged. First, due to the nature of the intervention, blinding of participants and investigators was not possible in any of the trials, while minor deviations from intended interventions were also noted in three trials, leading to some quality concerns during risk of bias assessment. Second, the trials, separately, included a modest number of patients, and selection criteria were not identical in all of them, allowing the inclusion of patients based on volumetric methods in two trials and also leading to significant imbalances among the included studies (but not between the two treatment arms). Furthermore, only one trial had international participation, while recruitment was limited in the USA, Japan or Asia in the other three trials. These differences in study design and selection criteria may interfere with the generalisability of the reported findings; yet, no significant heterogeneity was evident in the analysis of the outcomes. An individual patient data meta-analysis (mechanical thrombectomy for large brain infarction, MAGNA collaboration), rather than a study-level meta-analysis, with the potential to adjust for baseline differences among the included patients, centrally adjudicate imaging data and outcome events, and analyse specific patients' subgroups is warranted to provide more robust evidence. Finally, data extraction for TESLA trial was based on unpublished yet presented results during an international conference (European Stroke Organisation Conference 2023)[7] and minimal variations in relation to the future peer-reviewed publication cannot be excluded.

CONCLUSIONS

In conclusion, the current meta-analysis provides promising results that EVT is safe and effective and may be considered

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Study	logOR	SE	Weight	Odds Ratio IV, Random, 95% CI
ANGEL-ASPECT	0.49	0.17	36.4%	1.63 [1.17, 2.28]
RESCUE-Japan LIMIT	0.88	0.26	15.6%	2.41 [1.45, 4.01]
SELECT2	0.53	0.20	26.3%	1.70 [1.15, 2.51]
TESLA	0.34	0.22	21.7%	1.40 [0.91, 2.16]
Total (95% CI)			**100.0%**	**1.70 [1.39, 2.07]**

Heterogeneity: Tau^2 = 0; Chi^2 = 2.61, df = 3 (P = .46); I^2 = 0%
Test for overall effect: Z = 5.15 (P < .01)

Favors BMT   Favors EVT
shift analysis

B

Study	EVT Events	EVT Total	BMT Events	BMT Total	Weight	Risk Ratio IV, Random, 95% CI
ANGEL-ASPECT	108	230	75	225	39.8%	1.41 [1.12, 1.77]
RESCUE-Japan LIMIT	31	100	13	102	13.0%	2.43 [1.35, 4.37]
SELECT2	67	178	32	174	25.3%	2.05 [1.42, 2.95]
TESLA	45	152	29	148	22.0%	1.51 [1.00, 2.27]
Total (95% CI)		**660**		**649**	**100.0%**	**1.69 [1.33, 2.14]**

Heterogeneity: Tau^2 = 0.023; Chi^2 = 4.94, df = 3 (P = .18); I^2 = 39%
Test for overall effect: Z = 4.34 (P < .01)

Favors BMT   Favors EVT
mRS 0-3

C

Study	EVT Events	EVT Total	BMT Events	BMT Total	Weight	Risk Ratio IV, Random, 95% CI
ANGEL-ASPECT	69	230	26	225	47.7%	2.60 [1.72, 3.92]
RESCUE-Japan LIMIT	14	100	8	102	11.9%	1.79 [0.78, 4.07]
SELECT2	36	178	12	174	21.1%	2.93 [1.58, 5.45]
TESLA	22	152	13	148	19.3%	1.65 [0.86, 3.15]
Total (95% CI)		**660**		**649**	**100.0%**	**2.33 [1.76, 3.10]**

Heterogeneity: Tau^2 = 0; Chi^2 = 2.30, df = 3 (P = .51); I^2 = 0%
Test for overall effect: Z = 5.84 (P < .01)

Favors BMT   Favors EVT
mRS 0-2

D

Study	EVT Events	EVT Total	BMT Events	BMT Total	Weight	Risk Ratio IV, Random, 95% CI
ANGEL-ASPECT	28	230	26	225	52.0%	1.05 [0.64, 1.74]
RESCUE-Japan LIMIT	5	100	3	102	10.3%	1.70 [0.42, 6.93]
SELECT2	11	178	3	174	12.6%	3.58 [1.02, 12.63]
TESLA	14	152	8	148	25.2%	1.70 [0.74, 3.94]
Total (95% CI)		**660**		**649**	**100.0%**	**1.46 [0.91, 2.33]**

Heterogeneity: Tau^2 = 0.045; Chi^2 = 3.65, df = 3 (P = .30); I^2 = 18%
Test for overall effect: Z = 1.57 (P = .12)
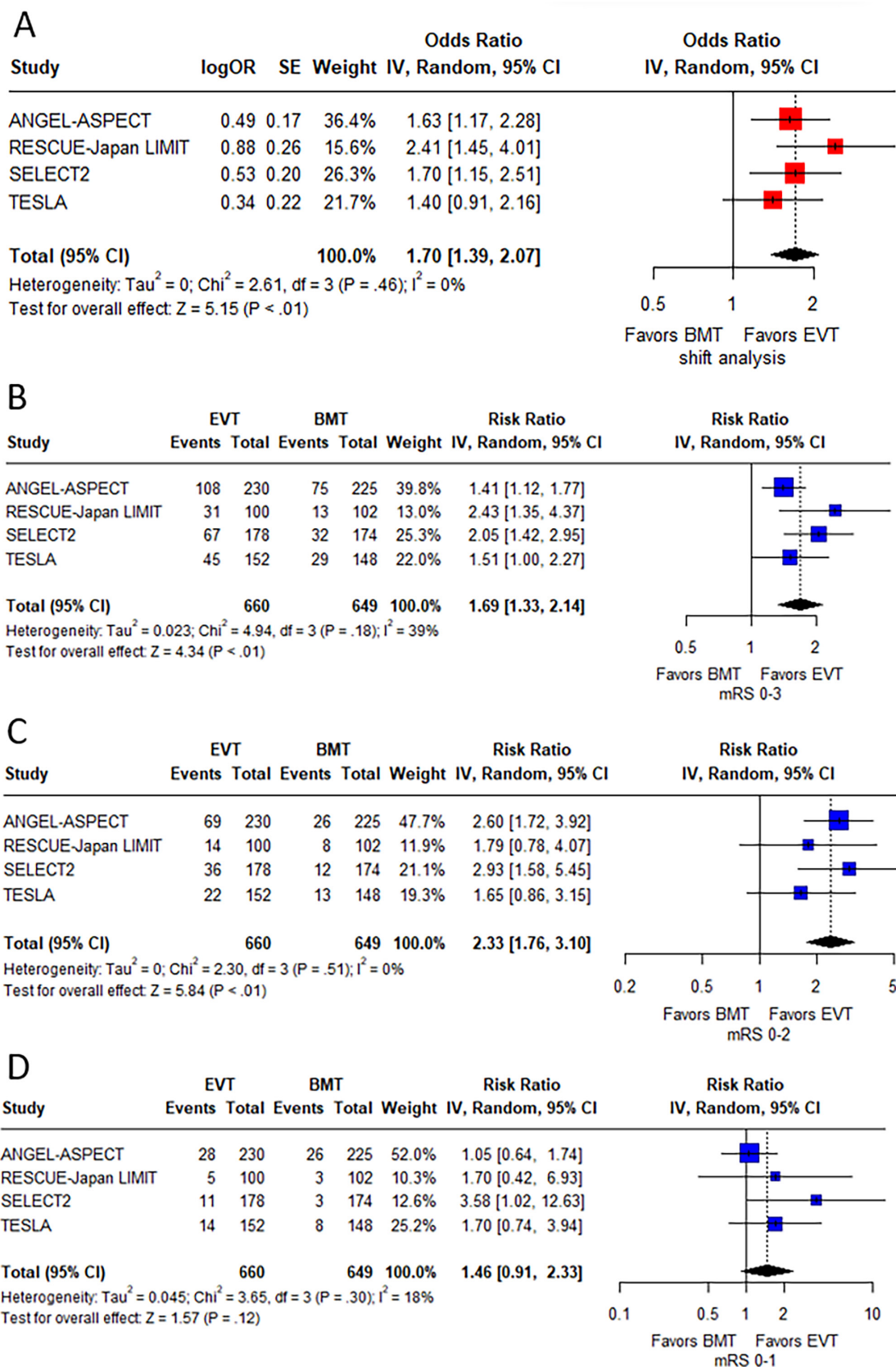
Favors BMT   Favors EVT
mRS 0-1

Figure 1   Analysis of efficacy outcomes. forest plot presenting the association of EVT compared with BMT with reduced disability (panel a), independent ambulation (B), good functional outcome (panel C) and excellent functional outcome (D) at 3 months. ANGEL-ASPECT, Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; BMT, best medical treatment; EVT, endovascular treatment; IV, inverse variance; mRS, Modified Rankin Scale; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large Ischemic core Trial; SELECT2, Randomised Controlled Trial to Optimize Patient Selection for Endovascular Treatment in Acute Ischemic Stroke; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke.

in everyday clinical practice in patients with large-core AIS, as assessed by an ASPECTS of 2–5 or volumetric methods.

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