Endovascular treatment for anterior circulation large-vessel occlusion ischemic stroke with low ASPECTS: a systematic review and meta-analysis

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Abstract

Background: Endovascular treatment (EVT) for acute ischemic stroke (AIS) patients presenting with Alberta Stroke Program Early CT Score (ASPECTS) 0–5 has not yet proven safe and effective by clinical trials.

Objectives: The aim of the study was to assess whether EVT in AIS patients presenting with low ASPECTS is beneficial.

Design: Systematic review and meta-analysis of available studies in accordance with the PRISMA statement.

Data sources and Methods: We have searched MEDLINE, the Cochrane Central Register of Controlled Trials, and reference lists of articles published until 28 May 2022 with the aim to calculate (1) modified Rankin scale (mRS) score 0–3 at 3 months, (2) mRS score 0–2 at 3 months, (3) symptomatic intracranial hemorrhage (sICH), and (3) mortality at 3 months.

Results: Overall, 24 eligible studies were included in the meta-analysis, comprising a total of 2539 AIS patients with ASPECTS 0–5 treated with EVT. The pooled proportion of EVT-treated patients achieving mRS 0–3 at 3 months was calculated at 38.4%. The pooled proportion of EVT-treated patients achieving mRS 0–2 at 3 months was 25.7%. Regarding safety outcomes, sICH occurred in 12.8% of patients. The 3-month pooled mortality was 30%. In pairwise meta-analysis, patients treated with EVT had a higher likelihood of achieving mRS 0–3 at 3 months compared with patients treated with best medical therapy (BMT, OR: 2.41). sICH occurred more frequently in EVT-treated patients compared with the BMT-treated patients (OR: 2.30). Mortality at 3 months was not different between the two treatment groups (OR: 0.71).

Conclusion: EVT may be beneficial for AIS patients with low baseline ASPECTS despite an increased risk for sICH. Further data from randomized-controlled clinical trials are needed to elucidate the role of EVT in this subgroup of AIS patients.

Registration: The protocol has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO; Registration Number: CRD42022334417.

Keywords: ASPECTS, endovascular treatment, large-vessel occlusion, modified Rankin scale, mortality, stroke, symptomatic intracranial hemorrhage

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Introduction

Acute ischemic stroke (AIS) treatment aims at rapid reperfusion of oligemic brain tissue, using two established recanalization therapies: intravenous thrombolysis (IVT) and endovascular treatment (EVT).[1] IVT has been shown to reduce

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disability in eligible AIS patients up to 4.5 h from symptom onset using standard neuroimaging and up to 9 h using advanced neuroimaging.[2] A main predictor of AIS outcome[3] and treatment efficacy[4] is infarct core volume at baseline. Baseline CT hypoattenuation of greater than one-third of the middle cerebral artery (MCA) territory has been an exclusion criterion for some – but not all – IVT clinical trials and, according to most recent American Heart Association/ American Stroke Association (AHA/ASA) guidelines, no benefit from thrombolytic treatment has been proven in this subgroup of AIS patients.[5] The European Medicine Agency advises against treatment with alteplase in 'Patients with severe stroke' [as assessed clinically (NIHSS score >2) or by appropriate imaging] because 'patients with very severe stroke are at higher risk for intracerebral hemorrhage and death'.[6] European Stroke Organization (ESO) guidelines follow a different approach, highlighting the fact that there is no evidence that extensive ischemic changes on baseline imaging modify the treatment effect of IVT.[7,8] However, they note a significant interaction between the presence of early ischemic changes on baseline CT and mortality after IVT treatment. In conclusion, they provide a weak recommendation in favor of IVT based on very low quality of evidence within 4.5 h from last seen well (LSW).[9] As practically all AIS patients with large ischemic core suffer from large-vessel occlusion (LVO), EVT can be used in conjunction with IVT or as a standalone therapy in otherwise eligible large ischemic core patients. However, patients with extensive infarcts at baseline were excluded by many EVT clinical trials while international recommendations advocate against EVT in LVO patients with low (<6) Alberta Stroke Program Early Computed Tomography Score (ASPECTS).[5,10]

To quantify the extent of hypodensities in baseline CT, ASPECTS has been developed for anterior circulation LVO stroke [internal carotid artery (ICA) or MCA).[11] Focal hypoattenuation of the cortex and in the basal ganglia, gray–white matter dedifferentiation and loss of the insular ribbon sign are assessed through a 10-point scoring system corresponding to anatomical regions that extend over the MCA arterial distribution: four subcortical [caudate (C), lentiform (L), internal capsule (IC), insular ribbon (I)] and six cortical areas spanning over the superficial MCA territory (M1–M6).[12] It was developed to quantify early ischemic changes (hypoattenuation, loss of gray–white matter distinction, or focal swelling) on baseline CT of AIS patients eligible for IVT arriving within 3 h from symptom onset. For each region presenting early ischemic changes, the overall score of 10 is reduced by 1. The goal was to develop practical prediction tools of functional independence, dependence, and symptomatic intracranial hemorrhage (sICH) after thrombolytic treatment. In the seminal paper, ASPECTS <8 almost excluded functional independence of AIS patients post IVT, and ASPECTS showed inverse correlation with mortality, reaching 50% for scores 0–2.[11] ASPECTS never gained wide acceptance as a prognostic tool and failed to substitute the exclusion criterion of hypodensity in more than one-third of MCA territory for IVT. However, it gained momentum in the clinical trials of EVT; most of the five first positive EVT trials used an ASPECTS cut-off of 6 to include patients for randomization.[10,13] Positive results led AHA/ASA and ESO guidelines to provide IA level evidence for EVT in patients with an ASPECTS of 6 or greater.[5,10] As a consequence, low ASPECTS is considered any score below 6, corresponding to large core infarcts, for which there is currently no strong recommendation for EVT.

A previous meta-analysis of observational studies has indicated that EVT for low ASPECTS is associated with improved functional independence and lower mortality at 90 days without significant increase in sICH compared with the best medical treatment (BMT), across various definitions, thresholds of large core size, and time windows. EVT was associated with significantly higher odds of functional independence (EVT: 25% *versus* BMT: 7%) and lower likelihood of mortality (EVT: 20% *versus* BMT: 30%) at 90 days, whereas the odds of sICH were similar (EVT: 9% *versus* BMT: 5%).[14] Better functional outcomes have been reported from another systematic review and meta-analysis (EVT: 28% *versus* 4% with BMT), with similar rates of mortality (EVT: 31% *versus* BMT: 37%) and sICH (EVT: 9% *versus* BMT: 6%).[15] Similar results have been reported from three other meta-analyses, assessing ASPECTS, pre-treatment infarct core volume, or both[16–18] (Supplemental **eTable 1**). Since the publication of these analyses, the experience from large multicenter registries and one randomized-controlled clinical trial (RCT) has been published, providing exciting new data on this subgroup of LVO AIS patients, justifying an updated systematic review

and meta-analysis. The current meta-analysis differs from previously published meta-analyses on the topic as we have excluded LVO patients presenting with ASPECTS of 6, given the fact that EVT has a strong recommendation (level 1/ grade A) for this specific LVO subgroup.

Methods

Standard protocol approvals, registrations, and patient consents

The pre-specified protocol of the present systematic review and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; Registration No. CRD42022334417). The meta-analysis is reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[19] and data are presented according to the Meta-Analysis of Observational Studies Epidemiology (MOOSE) proposal.[20] This study did not require an ethical board approval or written informed consent by the patients according to the study design (systematic review and meta-analysis).

Data sources, searches, and study selection

A systematic literature search was conducted to identify eligible studies reporting on patients with AIS due to LVO and ASPECTS $\leqslant 5$ treated with EVT [intra-arterial thrombolysis and mechanical thrombectomy (MT)]. The literature search was performed independently by three authors (A.S., L.P., and G.T.). We searched MEDLINE and Scopus, using search strings that included the following terms: 'stroke', 'low ASPECTS', and 'endovascular treatment'. The complete search algorithms used in MEDLINE and Scopus are provided in the **eMethods** in the Supplement. No language or other restrictions were applied. Our search spanned from inception of each database to 28 May 2022, for each electronic database. We additionally searched reference lists of published articles manually to ensure the comprehensiveness of bibliography.

RCTs and meta-analyses of RCT-derived individual patient data, and observational studies (prospective or retrospective) reporting on the outcomes of AIS patients with large core infarction treated with EVT were considered eligible. Only studies including LVO patients with occlusion of the anterior circulation (ICA/MCA occlusions) that calculated baseline ASPECTS using CT, MRI, or both were considered. We have not considered studies that define large core infarcts using volumetry, to reduce variability of data, as there is no volumetric cut-off for ASPECTS 6 and different methods may be used for volumetry. Any EVT technique was accepted, stent-retriever thrombectomy, thromboaspiration or other, and registries of specific medical devices used in EVT were also included. Either single-arm studies or studies with a comparative arm including patients who received BMT (with or without IVT) as the control group were considered. Commentaries, editorials, narrative reviews, and case reports were excluded. Among the studies presenting duplicate data, the ones with the largest dataset were retained while the others were excluded. All retrieved studies were independently assessed by two authors (A.S. and L.P.), and any disagreements were resolved after discussion with a third tie-breaking author (G.T.).

Quality control, bias assessment, and data extraction

Eligible studies were subjected to quality control and bias assessment employing the Cochrane risk-of-bias (RoB 2) tool for RCTs,[21] the Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) tool for systematic reviews and individual patient data meta-analyses,[22] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for the observational studies.[23] Quality control and bias assessment were conducted independently by two reviewers (A.S. and L.P.), and disagreements were settled by consensus after discussion with the corresponding author (G.T.).

Data extraction was performed in structured reports, including author names, date of publication, study design, country, number of included AIS patients, patients' characteristics, and outcome events.

Outcomes

An aggregate data meta-analysis was performed with the inclusion of the identified studies. The primary outcome of interest was the pooled proportion of EVT-treated patients achieving a modified Rankin scale (mRS) score 0–3 at 3 months by analyzing data included in both single-arm and

comparative studies. A co-primary outcome of interest was the likelihood of achieving mRS score 0–3 at 3 months among patients treated with EVT compared with patients receiving BMT. For this outcome, the analysis was restricted to studies presenting a comparative BMT arm.

Secondary outcomes of interest comprised (1) mRS score 0–2 at 3 months, (2) sICH, and (3) mortality at 3 months. Baseline characteristics of patients, including sex, age, National Institutes of Health Stroke Scale (NIHSS) score, ASPECTS, and IVT pre-treatment, were also analyzed. All outcomes were assessed after stratification by study design (meta-analyses, RCTs, prospective registries, or retrospective cohorts). The second sensitivity analysis was conducted stratified by the baseline ASPECTS score (3–5 *versus* 0–2).

Statistical analysis

For the aggregate meta-analysis, we calculated for each dichotomous outcome of interest the corresponding pooled proportions with 95% confidence intervals (95% CI), after the implementation of the variance-stabilizing double-arcsine transformation. We also calculated the corresponding odds ratios (OR) with 95% CI for the comparison of dichotomous outcomes between patients treated with EVT compared with BMT. For studies reporting continuous outcomes in median values and corresponding interquartile ranges, we estimated the sample mean and standard deviation using the quantile estimation method. Continuous outcomes were assessed by mean difference (MD). The random-effects model of meta-analysis (DerSimonian and Laird) was used to calculate the pooled estimates.[24] Subgroup differences between different study designs were assessed by the Q-test for subgroups. A sensitivity analysis was performed by removing the studies that explicitly excluded patients with an ASPECTS of 5. Heterogeneity was assessed with the I^2 and Cochran's Q statistics. For the qualitative interpretation of heterogeneity, I^2 values $>50\%$ and values $>75\%$ were considered to represent substantial and considerable heterogeneity, respectively. The significance level for the Q statistic was set at 0.1. Publication bias across individual studies was assessed when more than four studies were included in the analysis of the outcomes of interest, using both funnel plot inspection and the Egger's linear regression test,[25] and the equivalent z-test for each pooled estimate with a two-tailed p-value <0.05 was considered statistically significant. As an exploratory analysis, meta-regression was performed for ASPECTS at admission, when this information was available in 10 or more of the studies that were included in the outcomes assessed.[26] Finally, the fragility index was calculated for the outcomes of the two-arm meta-analysis,[27] based on the classification by Mun *et al.*[28] suggesting that a fragility index $\leqslant 4$ was indicative of a non-robust result. All statistical analyses using the Cochrane Collaboration's Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014),[26] the OpenMetaAnalyst,[29] and R software version 3.5.0 (package: metafor).[30]

Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary information files.

Results

Literature search and included studies

The systematic database search yielded a total of 672 records from the MEDLINE and Scopus databases, after the exclusion of potential duplicates (Figure 1). After initial screening, we retrieved the full text of 68 records that were considered potentially eligible for inclusion, and after reading the full-text articles, 14 were further excluded (Supplemental **eTable 2**). Finally, we identified 24 eligible studies for inclusion, of which 1 was an individual patient data (IPD) meta-analysis of RCT-derived data conducted by the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaborators,[31] 2 were RCTs not included in the previous meta-analysis,[32,33] 16 were observational studies based on prospectively collected data (prospective registries),[34–49] and 5 were retrospective cohort studies (Table 1),[50–54] comprising a total of 2539 AIS patients with low ASPECTS score treated with EVT.

Quality control of included studies

The risk of bias assessment regarding the included IPD meta-analysis was performed using the Assessing the Methodological Quality of Systematic Reviews

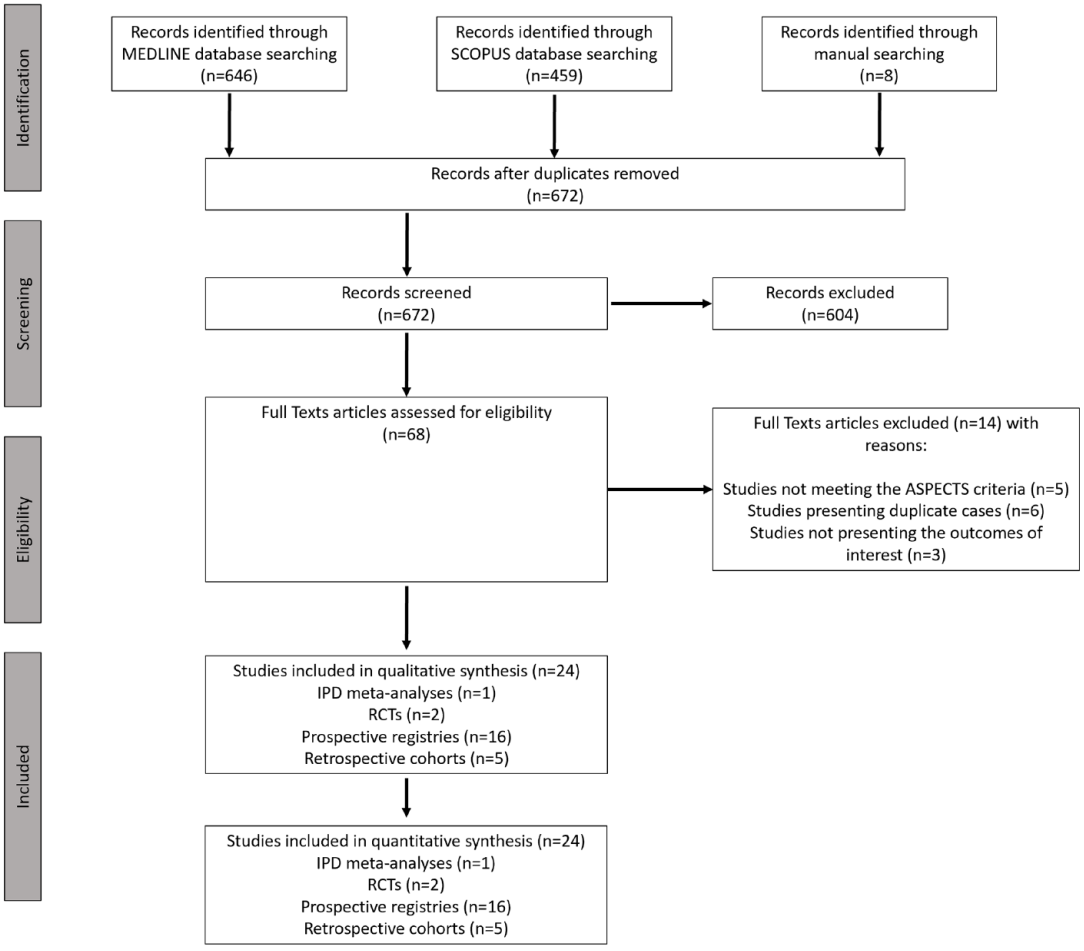

Figure 1. Flow chart presenting the selection of eligible studies.

(AMSTAR 2) tool and is presented in Supplemental **eTable 3**.[22] Román *et al.*[31] clearly described the methodology for conducting the IPD meta-analysis, while the risk of bias for the seven included RCTs was also adequately assessed. However, the specific reasons for study exclusion, the sources of funding in the included trials, and the evaluation of publication bias were not thoroughly discussed. The overall quality was evaluated at 81% (13 out of 16 criteria were fulfilled).

The risk of bias in included RCTs was assessed by the Cochrane RoB 2 tool and is presented in Supplemental **eFigures 1–2**. The randomization process was not reported in the study of Hill *et al.*[32] while Yoshimura *et al.*[33] did not clearly report whether a blinded assessment was performed for the evaluation of clinical outcomes. Both studies were open-label, presenting high risk of performance bias. Overall, the included RCTs were considered of moderate quality with substantial risk of bias.

The risk of bias in the included observational studies was assessed by the ROBINS-I tool and is presented in Supplemental **eFigures 3–4**. Overall, 16 studies were not controlled;[34,35,37–41,43,45,46,48,49,51–54] therefore, the assessment of confounding bias, bias in the classification of intervention, and bias due to deviations from intended interventions were not applicable. Yet, significant confounding bias was detected in all five controlled studies as there were several baseline differences between the patients' groups (EVT-treated *versus* BMT-treated).[36,42,44,47,50] Exclusive inclusion of patients who underwent brain MRI for the ascertainment of ASPECTS was the source of moderate selection bias in seven studies.[37–39,41,46,52,53] Only five studies reported a blinded outcome assessment performed by investigators not involved in the acute management of LVO patients.[38,40,41,46,51]

Table 1. Main characteristics of studies included in the systematic review ($n = 24$).

Author	Type of study	Country	Period of recruitment	No. of centers	No. of EVT	No. of BMT	Imaging modality	Outcomes assessed	Main inclusion criteria
ASPECTS < 6									
Jiang *et al.*[40]	Retrospective	China	2010–2015	2	36	32	CT	mRS, sICH, mortality	NIHSS ⩾ 10, age < 80 years
Derraz *et al.*[38]	Retrospective	France	2012–2017	1	139		MRI	mRS, ENI, sICH, mortality	Visible FVHs on baseline FLAIR
Song *et al.*[53]	Retrospective	China	2016–2018	1	19		MRI	mRS, sICH, mortality	< 6 h, or < 12 h and ASL-DWI mismatch
Manceau *et al.*[52]	Retrospective	France	2010–2016	1	82		MRI	mRS, TICI, PH2, mortality	
Inoue *et al.*[39]	Retrospective	France	2007–2013	1	75		MRI	mRS, TIMI, DWI volume, sICH, mortality	
Kim *et al.*[43]	Retrospective	Korea	2010–2013	1	22		MRI	mRS, mTICI, sICH, mortality	DWI-ASPECTS 4–5, treatment < 6 h, NIHSS > 4, target mismatch multimodal MR infarct volume < 1/3 of MCA.
Lei *et al.*[51]	Retrospective	China	2016–2019	1	152		CT	mRS, mTICI, sICH, mortality	
Xing *et al.*[54]	Retrospective	China Naval, Shanghai	2018–2019	1	60		CT	mRS, c-ASPECTS, sICH, mortality	Treatment < 24 h
Broocks *et al.*[36]	Prospective	Germany Hamburg	2015–2019	1	99	71	CT	mRS, TICI, PH2, mortality	
Panni *et al.*[46]	Prospective registry (ETIS)	France	2012–2017	5	291		MRI	mRS, mTICI, sICH, mortality	Treatment < 6 h
Almallouhi *et al.*[34]	Prospective registry (STAR)	Multinational	2016–2020	28	213		CT	mRS, mTICI, sICH, mortality	ASPECTS 2–5, treatment < 24 h
Zaidat *et al.*[49]	Prospective registry (STRATIS)	USA	2014–2016	55	57		CT	mRS, mTICI, sICH, mortality	Treatment < 8 h
Kaesmacher *et al.*[41]	Retrospective registry (BEYOND-SWIFT)	European	2010–2017	7	237		33% CT 66% MRI	mRS, mTICI, sICH, mortality	Use of the Solitaire thrombectomy device
Deguchi *et al.*[37]	Prospective registry (RESCUE-Japan Registry)	Japan	2010–2011	Multi-center	32		MRI	mRS, sICH, mortality	Treatment < 8 h, full recanalization after EVT
Kakita *et al.*[42]	Prospective registry (RESCUE-Japan Registry 2)	Japan	2014–2016	46	172	332	MRI 91%	mRS, ENI, TICI, sICH, mortality	Pre-stroke mRS ⩽ 1

(Continued)

Table 1. (Continued)

Author	Type of study	Country	Period of recruitment	No. of centers	No. of EVT	No. of BMT	Imaging modality	Outcomes assessed	Main inclusion criteria
Sarraj *et al.*[47]	Prospective registry (SELECT)	USA	2016–2018	9	37	34	CT	mRS, infarct growth, FIV, sICH, mortality	
Jia *et al.*[40]	Prospective registry (ANGEL-ACT)	China	2017–2019	111	91		CT	mRS, mTICI, sICH, PH2, mortality	
Meyer *et al.*[44]	Prospective registry (GSR-ET)	Germany	2015–2018	25	124	124	CT	mRS, mTICI, sICH, mortality	Propensity score matching
Bouslama *et al.*[35]	Prospective registry (GESTOR)	USA	2010–2020	1	125		CT	mRS, mTICI, PH, FIV, hemicraniectomy, mortality	
Ospel *et al.*[45]	Prospective registry (MR CLEAN Registry)	Netherlands	2014–2017	16	268		CT	mRS, eTICI, sICH, mortality	
Román *et al.*[31]	RCT meta-analysis (HERMES)	Multinational			109	116		mRS	
Yoshimura *et al.*[33]	RCT	Japan	2018–2021	45	101	102	MRI 86%	mRS, TICI, sICH, mortality	DWI-ASPECTS 3–5, eight patients were adjudicated misclassified as ASPECTS 0–2
ASPECTS 0–4									
Yoo *et al.*[48]	Prospective registry (PICS/Pivotal)	USA, Canada	2008–2010		40		CT	mRS, TIMI, sICH, ICH, mortality	Penumbra stroke system, patients with > 1/3 MCA hypodensity were excluded
Hill *et al.*[32]	Subgroup analysis of RCT (IMS-III)	USA, Canada, Europe	2008–2013	58	57	35	CT	mRS, sICH, mortality	All patients received IVT, first-generation thrombectomy devices and IA thrombolysis used
Román *et al.*[31]	RCT meta-analysis (HERMES)	Multinational			57	69	MRI 52%	mRS, sICH, mortality	

ASL, arterial spin labeling; c-ASPECTS, cortical ASPECTS; DWI, diffusion-weighted imaging; ENI, neurological improvement of 8 or more points on the NIHSS or an NIHSS score of 0–1 at 24 h; eTICI, expanded TICI; FIV, final infarct volume; FLAIR, fluid-attenuated inversion recovery; FVH, FLAIR vascular hyperintensity (represents slow blood flow in leptomeningeal collaterals); IA, intra-arterial; MCA, middle cerebral artery; mTICI, modified TICI; PH2, parenchymal to the hematoma type 2, according to European Cooperative Acute Stroke Study 3 classification; NA, not applicable; NR, not reported; SD, standard deviation; sICH, any intracerebral hemorrhage on imaging with an increase in at least 4 NIHSS points within 24 h or resulting in death within 24 h after intervention; TICI, thrombolysis in cerebral infarction; TIMI, thrombolysis in myocardial infarction, a score of 3 suggests complete recanalization.

Table 2. Overview of analyses for primary and secondary outcomes.

Variable	Single-arm analysis			Two-arm analysis			
	No. of studies	Pooled estimates (95% CI)	I^2, p for Cochran's Q	No. of studies	OR (95% CI)	I^2, p for Cochran's Q	Fragility index
Primary outcome							
mRS 0–3 at 3 months	12	38.4% (34.4–42.6%)	60%; 0.004	5	2.41 (1.13–5.13)	84%; <0.001	5
Secondary outcomes							
mRS 0–2 at 3 months	23	25.7% (22.4–29.1%)	70%; <0.001	7	2.91 (1.51–5.61)	62%; 0.020	10
sICH	19	12.8% (9.4–16.7%)	83%; <0.001	6	2.30 (1.18–4.48)	45%; 0.110	3
Mortality at 3 months	21	30% (25.2–35.1%)	85%; <0.001	6	0.71 (0.42–1.21)	72%; 0.003	12

CI, confidence interval; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.

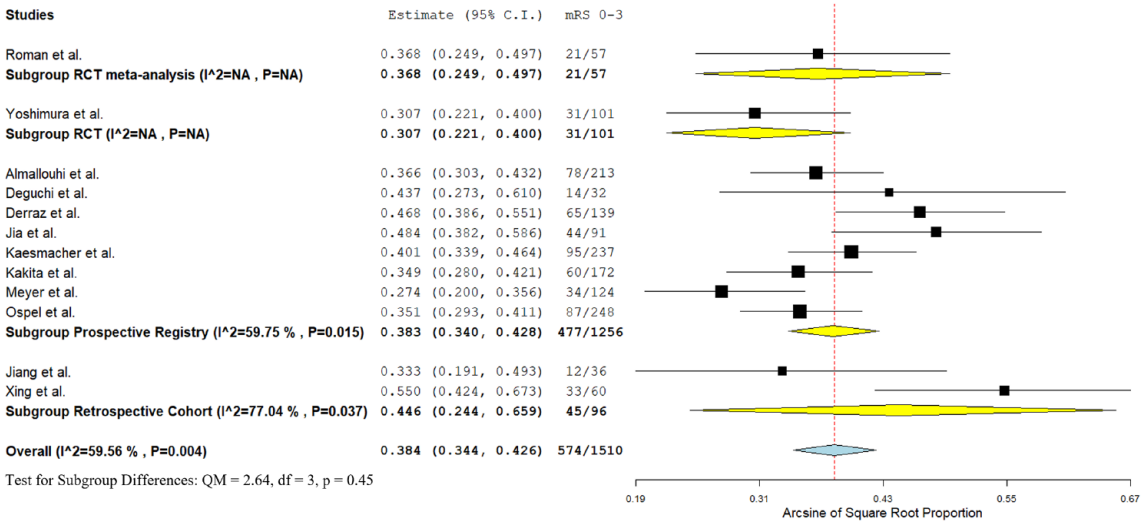

Figure 2. Forest plot presenting the pooled proportion of EVT-treated patients achieving mRS 0–3 at 3 months, stratified by study design.

Quantitative analyses

An overview of analyses for all primary and secondary outcomes is summarized in Table 2. It should be noted that cases presented by Broocks *et al.*[36] were also included in the study of Meyer *et al.*[44] Consequently, we failed to include both studies in the analyses of same outcomes, while the study by Broocks *et al.*[36] was only included in the analysis of mRS 0–2 outcome, where no overlapping data from Meyer *et al.*[44] had been reported.

Single-arm meta-analysis, stratified by study design. The pooled proportion of EVT-treated patients achieving mRS 0–3 at 3 months was calculated at 38.4% (95% CI: 34.4–42.6%; 12 studies; $I^2 = 60\%$; p for Cochran's $Q = 0.004$; p for subgroup differences = 0.45; Figure 2). The pooled proportion remained almost identical in the sensitivity analysis that was performed by removing the studies that excluded patients presenting with an ASPECTS of 5 (Supplemental **eFigure 5**).

With regard to the secondary outcomes, the pooled proportion of EVT-treated patients achieving mRS 0–2 at 3 months was 25.7% (95% CI: 22.4–29.1%; 23 studies; $I^2 = 70\%$; p for Cochran's $Q < 0.001$; p for subgroup differences = 0.02; Supplemental **eFigure 6**). Significant subgroup

differences were mostly driven by the included recent RCTs[31,32] and were also retained in the sensitivity analysis (Supplemental **eFigure 7**). Almost 13% of the patients developed sICH (12.8%; 95% CI: 9.4–16.7%; 19 studies; $I^2 = 83\%$; p for Cochran's $Q < 0.001$; p for subgroup differences = 0.08; Supplemental **eFigure 8**). A slightly lower proportion was noted in the sensitivity analysis (12.3%; 95% CI: 8.8–16.3%; Supplemental **eFigure 9**). The pooled 3-month mortality was calculated at 30% (95% CI: 25.2–35.1%; 21 studies; $I^2 = 85\%$; p for Cochran's $Q < 0.001$; p for subgroup differences = 0.06; Supplemental **eFigure 10**); the rate of 3-month mortality was practically identical in the sensitivity analysis (29%; 95% CI: 24–34.1%; Supplemental **eFigure 11**).

Publication bias was evaluated using funnel plots for every outcome of the analysis. Asymmetry or evidence of small study effects (i.e. publication bias) were uncovered through funnel plot inspection, but were not confirmed by the Egger's linear regression test for any of the reported single-arm outcomes (Supplemental **eFigures 12–15**).

The baseline characteristics of the included patients are presented as follows: 55% were men, the mean age was 68 years, the mean NIHSS score at admission was 19 points, the mean ASPECTS was 4 points, and almost 40% of the patients were pre-treated with IVT (39.3%; 95% CI: 30.4–48.5%; 17 studies; $I^2 = 94\%$; p for Cochran's $Q < 0.001$; p for subgroup differences < 0.01; Supplemental **eFigures 16–20**).

Meta-regression analysis for ASPECTS at admission could not be performed for the primary outcome as less than 10 studies reported this information. No significant interaction between ASPECTS at admission and any of the secondary outcomes was noted (Supplemental **eFigures 21–23**); yet, higher ASPECTS showed a trend to higher likelihood of achieving mRS 0–2 at 3 months ($p = 0.076$).

Pairwise meta-analysis, stratified by study design. Patients treated with EVT had significantly higher likelihood of achieving mRS 0–3 at 3 months compared with BMT-treated patients (OR: 2.41; 95% CI: 1.13–5.13; five studies; $I^2 = 84\%$; p for Cochran's $Q < 0.001$; Figure 3), with no significant subgroup differences among different study designs (p for subgroup differences = 0.35). Sensitivity analysis confirmed a similar result (Supplemental **eFigure 24**). However, the fragility index was calculated at 5 indicating a 'somewhat robust' result (Supplemental **eFigure 25**).[28]

EVT-treated patients also had higher odds of achieving mRS 0–2 at 3 months compared with BMT-treated patients (OR: 2.91; 95% CI: 1.51–5.61; seven studies; $I^2 = 62\%$; p for Cochran's $Q = 0.02$; p for subgroup differences = 0.10; Supplemental **eFigure 26**). This significant difference was further accentuated in sensitivity analysis (OR: 3.54; 95% CI: 1.97–6.39; Supplemental **eFigure 27**). The fragility index of this outcome was calculated at 10, suggesting a 'somewhat robust' result (Supplemental **eFigure 28**).[28]

Regarding safety outcomes, sICH occurred more often in EVT-treated patients compared with BMT-treated patients (OR: 2.30; 95% CI: 1.18–4.48; six studies; $I^2 = 45\%$; p for Cochran's $Q = 0.11$; p for subgroup differences = 0.68; Supplemental **eFigure 29**). The difference between the two treatment groups was attenuated and became non-significant in the sensitivity analysis (OR: 2.01; 95% CI: 0.97–4.16; Supplemental **eFigure 30**). The fragility of the result was also confirmed during fragility index assessment, which was calculated at only 3, indicative of a 'highly-fragile' result (Supplemental **eFigure 31**).[28]

Mortality at 3 months was not different between the two treatment groups (OR: 0.71; 95% CI: 0.42–1.21; six studies; $I^2 = 72\%$; p for Cochran's $Q = 0.003$; p for subgroup differences = 0.98; Supplemental **eFigure 32**) and this was also confirmed in the sensitivity analysis (Supplemental **eFigure 33**). This non-significant difference in mortality was 'somewhat robust', with a fragility index of 12 (Supplemental **eFigure 34**).[28]

Publication bias was not confirmed by the Egger's linear regression test for any of the analyzed outcomes, despite certain asymmetry disclosed during funnel plot inspection (Supplemental **eFigures 35–38**).

Baseline characteristics were also compared between the two treatment groups. Sex, age, baseline NIHSS, ASPECTS, and IVT pre-treatment were well balanced between the two groups (Supplemental **eFigures 39–43**).Data stratified by

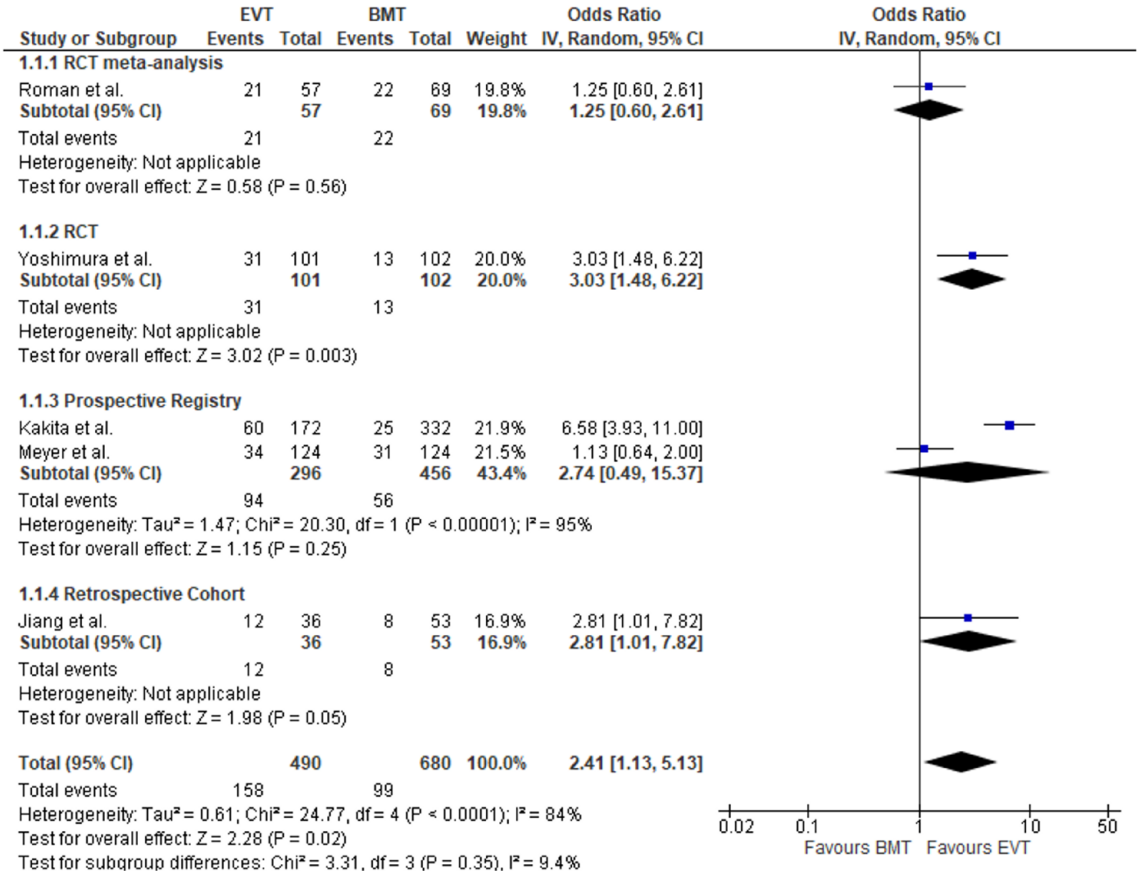

Figure 3. Forest plot presenting the OR of achieving mRS 0–3 at 3 months among patients treated with endovascular therapy *versus* patients treated with BMT stratified by study design.

ASPECTS score were available and could be extracted only for the outcome of mRS 0–2. According to the sensitivity analysis, no statistically significant difference was unraveled either in the single or the two-arm meta-analysis (Supplemental **eFigures 44 and 45**).

Discussion

The main findings of our meta-analysis indicate that 38.4% and 25.7% of patients with anterior circulation LVO and baseline ASPECTS 0–5 treated with EVT may reach mRS 0–3 and 0–2 at 3 months, respectively. A total of 12.8% patients developed sICH, while 30% of these died at 3 months. When EVT was compared with BMT, despite a significant increase in the odds of sICH, EVT was associated with better functional outcomes at 3 months quantified by mRS scores of 0–3 and 0–2. Heterogeneity in the primary outcome was considerable for both single-arm and pairwise analyses and could not be attributed to differences in the study design of included studies. Differences in time periods of recruitment, different stroke centers that may have used, in the absence of established guidelines, locally defined inclusion and exclusion criteria and differences in populations treated, may account for this heterogeneity, that has also been found in most secondary outcomes. No significant differences were found between the ASPECTS 3–5 and ASPECTS 0–2 either in the single or the two-arm meta-analysis due to the low number of patients treated with ASPECTS 0–2. It is of note that meta-analysis of the five two-arm studies that provided data for ASPECTS 3–5[31,33,42,44,47] favors EVT over BMT.

The strength of our study is that it incorporated many recently published papers from national and international registries, and the only published RCT that was specifically designed to compare EVT with BMT in LVO patients with low

ASPECTS (RESCUE-Japan).[33] A major limitation of this meta-analysis is that most studies were observational, some were single-arm, and others were single-center reports. The use of CT by some and MRI by others for measuring ASPECTS or, CT and MRI used interchangeably within the same study, represents another major limitation. Though ASPECTS interrater agreement and sensitivity increases with MRI as compared with CT, there is no clear consensus of how much damaged tissue is required for a region to be counted as affected.[54] DWI-ASPECTS is analogous but certainly not identical to standard ASPECTS.[55] In one of the few studies to compare DWI *versus* CT ASPECTS with minimal time delay between the examinations, DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS in patients with stroke within 3 h of symptom onset.[56] Almost all patients had CT-ASPECTS >5, limiting current knowledge for lower scores to transforming DWI-ASPECTS to CT-ASPECTS and vice versa. The same study also revealed that in the first 3 h post stroke, the sensitivity of CT early ischemic signs for IC and C is very low ($<20\%$), low ($<50\%$) for other areas, and moderate (50–60%) only for insular ribbon and M2. In many multicentre studies mentioned in this article, the DWI-ASPECTS 0–5 and CT-ASPECTS 0–5 were used as representing the same extend of ischemia that may represent an erroneous hypothesis. It would probably be closer to the truth to treat DWI-ASPECTS 0–4 and CT-ASPECTS 0–5 as analogous, but this is also a hypothesis not supported by any concrete data. In a more recent retrospective analysis of EVT cases that had both baseline CT and MRI, disagreement defined as CT ASPECTS ≥ 6 and DWI ASPECTS <6 has been shown to be quite frequent (20%).[57] In the subgroup of patients who had both imaging examinations within 1 h, median difference in ASPECTS was 1, but the difference ranged from -3 (DWI $>$ CT ASPECTS) to 5 (CT $>$ DWI ASPECTS). It is also clear that scoring discrepancy may be inversed: there are instances, such as relatively asymmetrical leukoencephalopathy, where ASPECTS on CT is lower than on DWI; 2% of patients fell into this category and there has even been a patient with ASPECTS 3 on CT who had scored 10 on DWI.

We have not performed an analysis of studies reporting baseline volumetry of AIS LVO patients as this is only a minority of studies and the fact that volumetry is performed using either DWI or CT perfusion maps (also using various imaging software which may produce different results) introduces unacceptable variability allowing no firm conclusions to be drawn by this aggregate data. However, reported volumetry data are of interest for putting into context the extensive variability of infarct volumes within the ASPECTS 0–5 group of AIS patients. EVT patients presenting with ASPECTS 0–5 who had baseline infarct volume >70 ml as measured by CT Perfusion tended to have higher rates of hemorrhagic transformation and hemicraniectomy, and had larger final infarct volumes as measured by DWI, compared with ASPECTS 0–5 patients with baseline infarct volume <70 ml.[35] These differences led to worse outcome at 90 days for the large core group, after adjusting for potential confounders. In addition, patients with the same score may also present with highly variable infarct volumes. A score of DWI-ASPECTS 5 has been found to correspond to 25–120 ml lesion volume; a score of 4 to 40–160 ml lesion volume; a score of 2 or 3 to 75–225 ml lesion volume; a score of 1 to 150–275 ml lesion volume.[58] This finding has been replicated, with increasing infarct volume variability with lower ASPECTS; DWI-ASPECTS 5 ranged 30–200 ml, significantly overlapping with DWI-ASPECTS 2, which corresponded approximately to volumes 100–275 ml in a recent study.[59] In another recent report, the median infarct volume with DWI-ASPECTS 5 was 81 ml ranging between 33 and 150 ml; DWI-ASPECTS 2 corresponded to a median ischemic volume of 150 ml ranging between 67 and 240 ml.[60] Such significant overlap between these quite distinct scores highlights the limits of ASPECTS for prognostication of LVO strokes. If these variations are consistently recorded through MRI, it is highly probable that ischemic core variations for every CT-ASPECTS number or range is even larger.[57] To further complicate things, DWI-ASPECTS may overestimate ischemic core in AIS patients, leading to exclusion from therapy of patients that could benefit from EVT. A recent analysis by the ETIS investigators revealed that 19% of 211 patients presenting with DWI-ASPECTS 0–5 had DWI reversal after EVT, especially when there has been successful recanalization.[61] The impact of imaging modality used to measure ASPECTS on clinical outcomes is elegantly illustrated by the study by Kaesmacher *et al.*,[41] in which EVT-treated 0–5 DWI-ASPECTS patients had better outcomes than EVT-treated 0–5

CT-ASPECTS patients. As we have included studies using either imaging modality or both, it should be acknowledged that this variation in ASPECTS assessment represents an additional methodological shortcoming of the current study. Finally, the result of our meta-analysis, similarly to the results of previous systematic reviews, refers mainly to higher ASPECTS in the spectrum of scores 0–5 and much less to very low ASPECTS (e.g. 0–2). In this specific ASPECTS subgroup, EVT may scarcely be associated with partial reversal of acute cerebral ischemia.[62]

It should also be kept in mind when interpreting the results of this meta-analysis that the intra- and interrater agreement of ASPECT has been reported to be moderately satisfactory.[63,64] The TENSION trial (ClinicalTrials.gov Identifier: NCT03094715) is currently randomizing patients with LVO presenting with ASPECTS 3–5, either on DWI or CT.[65] In an effort to standardize ASPECTS measurement, ASPECTS training using a web-based 'reading academy' is a prerequisite for a physician to randomize patients. A recent report of the scoring made by 100 TENSION investigators, who independently evaluated 20 CT scans as part of their qualification program for the study, challenges the effectiveness of this approach. Agreements for ASPECTS ratings were 28%, with interrater agreement of 13%; with more relaxed criteria (using the tolerance allowance according to TENSION inclusion criteria ranges: 0–2 *versus* 3–5 *versus* 6–10), the rate of agreement rose to 66%, still far from perfect.[66] Given all the aforementioned limitations of a semi-quantitative (ASPECTS) approach to select large core patients for EVT, it could be asserted that more information is needed in the acute phase to maximize EVT benefits and diminish risks for AIS patients. This information can be provided either by volumetry, which is a fully quantitative approach, or assessment of collaterals.

It appears that most patients with low ASPECTS have poor collaterals but as many as one-third may present with adequate collaterals.[67,68] When collateral status was assessed in low ASPECTS patients, those with poor collaterals had a median mRS score of 5 despite successful recanalization, while patients with good collaterals showed a median mRS score of 2 after successful recanalization.[69] A combined radiological score consisting of ASPECTS and collateral status (ASCO score) has been found superior to a CTP-based model for the prediction of good functional outcome in patients presenting with ASPECTS < 6.[70] In the Secondary Analysis of the Optimizing Patient's Selection for EVT in AIS (SELECT) study, discordance of ischemic core as measured by ASPECTS and low cerebral blood flow in perfusion maps was common; in discordant cases, a favorable CT Perfusion demonstrated a stronger association with good *versus* poor outcomes after EVT than a favorable CT.[47] In a multicentre, core-laboratory adjudicated, observational retrospective cohort study of the 'Jeunes en Neuroradiologie Interventionnelle Research Collaborative' (JENI-RC), the investigators examined the effect of treatment in AIS patients presenting with DWI-ASPECTS 0–6 and DWI volume ≥ 70 ml; a total of 130 AIS patients treated with EVT between 2015 and 2018 were compared with 42 AIS patients treated conservatively in the years before 2015.[71] EVT was associated with increased probability of favorable outcome and functional independence, as core perfusion mismatch ratio (CPRM) increased, and the difference became statistically significant with CPRM > 1.7. No difference in sICH rates was documented between the two groups. Fluid-attenuated inversion recovery vascular hyperintensities,[38] apparent Diffusion Coefficient Gradient Within Diffusion Lesions,[72] and incorporation of infarct location information on scoring[73] are currently studied to improve the prediction of treatment outcome in patients with large core infarctions. Most of these parameters are still exploratory hypotheses. Increasing complexity comes with a price. EVT is a life-saving procedure that has already reformed stroke networks around the world; too elaborate imaging will necessarily restrict interventions in a few stroke centers that cannot address the increasing demands for recanalization therapies. What is simple may be wrong; what is complicated may be unusable.[74]

There are two main factors to consider when selecting patients with large established brain infarctions for EVT: safety and futility. In an analysis of blood pressure after EVT (BEST) multicentre prospective registry of patients treated with EVT, low ASPECTS has been found to be the most important determinant of sICH: ASPECTS < 6 carried a statistically significant ($p = 0.009$) OR of 10 for sICH post EVT.[75] In addition, there are contradictory observations

regarding safety from the only RCT specifically recruiting large core patients[33] and the largest clinical registry that used propensity score matching.[44] The former demonstrates safety of the intervention for patients with DWI-ASPECTS 3–5, whereas the latter has shown worse outcomes with EVT for CT-ASPECTS 0–5, driven by more than double sICH rates compared with BMT. We should bear in mind that EVT may benefit low ASPECTS patients not only by salvaging brain tissue but also by reducing brain edema and malignant mass effect, leading to reduced rates of malignant infarctions and decompressive hemicraniectomies.[76]

In conclusion, the current meta-analysis provides data suggestive of clinical benefit of EVT despite an increase in the risk of sICH in LVO patients with low ASPECTS (0–5). Nevertheless, it should be acknowledged that most of these data refer to low (i.e. 3–5) but not very low (0–2) ASPECTS as the latter subgroup has been underrepresented in most included studies. Moreover, the overall quality of studies is low and more data from RCTs are urgently required. Currently, five RCTs are evaluating the safety and efficacy of EVT in patients with LVO and ASPECTS < 6: TENSION, NCT03094715; IN EXTREMIS-LASTE, NCT03811769; TESLA, NCT03805308; SELECT 2, NCT03876457; and ANGEL-ASPECT, NCT04551664. These studies will provide definitive data regarding the potential expansion of the indication of EVT in LVO patients with large core infarction.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Andrei Alexandrov: Validation; Writing – review & editing.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author (G.T.) on reasonable request.

Protocol registration

The protocol of this systematic review and meta-analysis has been registered to the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; Registration No. CRD42022334417).

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Supplemental material

Supplemental material for this article is available online.

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