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

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
disability in eligible AIS patients up to 4.5 h from symptom onset using standard neuroimaging and up to 9 h using advanced neuroimaging. A main predictor of AIS outcome and treatment efficacy 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. 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’. 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. 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). As practically all AIS patients with large ischemic core suffer from large-vascular occlusion (LVO), EVT can be used in conjunction with IVT or as a stand-alone 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). To quantify the extent of hypodensities in baseline CT, ASPECTS has been developed for anterior circulation LVO stroke (internal carotid artery (ICA) or MCA). 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). 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. 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. Positive results led AHA/ASA and ESO guidelines to provide IA level evidence for EVT in patients with an ASPECTS of 6 or greater. 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%). 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%). Similar results have been reported from three other meta-analyses, assessing ASPECTS, pre-treatment infarct core volume, or both (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.
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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 ≤ 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 \textit{et al.}\[^{28}\] suggesting that a fragility index \( \leq 4 \) 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...
(AMSTAR 2) tool and is presented in Supplemental eTable 3. Román et al. 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).

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

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. while Yoshimura et al. 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, 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). Exclusive inclusion of patients who underwent brain MRI for the ascertainment of ASPECTS was the source of moderate selection bias in seven studies. Only five studies reported a blinded outcome assessment performed by investigators not involved in the acute management of LVO patients.
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. | Retrospective | China | 2010–2015 | 2 | 36 | 32 | CT | mRS, sICH, mortality | NIHSS > 10, age < 80 years |
| Derraz et al. | Retrospective | France | 2012–2017 | 1 | 139 | | MRI | mRS, ENI, sICH, mortality | Visible FVHs on baseline FLAIR |
| Song et al. | Retrospective | China | 2016–2018 | 1 | 19 | | MRI | mRS, sICH, mortality | <6 h, or <12 h and ASL-DWI mismatch |
| Manceau et al. | Retrospective | France | 2010–2016 | 1 | 82 | | MRI | mRS, TICI, PH2, mortality | |
| Inoue et al. | Retrospective | France | 2007–2013 | 1 | 75 | | MRI | mRS, TIMI, DWI volume, sICH, mortality | |
| Kim et al. | 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. | Retrospective | China | 2016–2019 | 1 | 152 | | CT | mRS, mTICI, sICH, mortality | |
| Xing et al. | Retrospective | China Naval, Shanghai | 2018–2019 | 1 | 60 | | CT | mRS, c-ASPECTS, sICH, mortality | Treatment < 24 h |
| Broocks et al. | Prospective | Germany Hamburg | 2015–2019 | 1 | 99 | 71 | CT | mRS, TICI, PH2, mortality | |
| Panni et al. | Prospective registry | France | 2012–2017 | 5 | 291 | | MRI | mRS, mTICI, sICH, mortality | Treatment < 6 h |
| Almallouhi et al. | Prospective registry | Multinational | 2016–2020 | 28 | 213 | | CT | mRS, mTICI, sICH, mortality | ASPECTS 2–5, treatment < 24 h |
| Zaidat et al. | Prospective registry | USA | 2014–2016 | 55 | 57 | | CT | mRS, mTICI, sICH, mortality | Treatment < 8 h |
| Kaesmacher et al. | Prospective registry | European | 2010–2017 | 7 | 237 | | CT 66% MRI | mRS, mTICI, sICH, mortality | Use of the Solitaire thrombectomy device |
| Deguchi et al. | Prospective registry | Japan | 2010–2011 | Multi-center | 32 | | MRI | mRS, sICH, mortality | Treatment < 8 h, full recanalization after EVT |
| Kakita et al. | Prospective registry | Japan | 2014–2016 | 46 | 172 | 332 | MRI 91% | mRS, ENI, TICI, sICH, mortality | Pre-stroke mRS ≤ 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.   | Prospective registry [SELECT] | USA | 2016–2018 | 9 | 37 | 34 | CT | mRS, infarct growth, FIV, sICH, mortality |                     |
| Jia et al.      | Prospective registry [ANGEL-ACT] | China | 2017–2019 | 111 | 91 | CT | mRS, mTICI, sICH, PH2, mortality |                     |
| Meyer et al.    | Prospective registry [G5R-ET] | Germany | 2015–2018 | 25 | 124 | 124 | CT | mRS, mTICI, sICH, mortality | Propensity score matching                     |
| Bouslama et al. | Prospective registry [GESTOR] | USA | 2010–2020 | 1 | 125 | CT | mRS, mTICI, PH, FIV, hemicraniectomy, mortality |                     |
| Ospel et al.    | Prospective registry [MR CLEAN Registry] | Netherlands | 2014–2017 | 16 | 268 | CT | mRS, eTICI, sICH, mortality |                     |
| Román et al.    | RCT meta-analysis [HERMES] | Multinational | | | | | | mRS |                     |
| Yoshimura et al. | 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**

| Author          | Type of study | Country       | Period of recruitment | No. of centers | No. of EVT | No. of BMT | Imaging modality | Outcomes assessed                        | Main inclusion criteria                                      |
|-----------------|---------------|---------------|-----------------------|----------------|------------|------------|-----------------|------------------------------------------|-------------------------------------------------------------|
| Yoo et al.      | 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.     | 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.    | 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 24h; eTICI, expanded TICI; FIV, final infarct volume; FLAIR, fluid-attenuated inversion recovery; FHV, 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.
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. were also included in the study of Meyer et al. Consequently, we failed to include both studies in the analyses of same outcomes, while the study by Broocks et al. was only included in the analysis of mRS 0–2 outcome, where no overlapping data from Meyer et al. 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; I² = 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; I² = 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 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; \(F = 83\%\); \(p\) 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; \(F = 85\%\); \(p\) 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; \(F = 94\%\); \(p\) 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; \(F = 84\%\); \(p\) 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).

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; \(F = 62\%\); \(p\) 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).

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; \(F = 45\%\); \(p\) 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).

Mortality at 3 months was not different between the two treatment groups (OR: 0.71; 95% CI: 0.42–1.21; six studies; \(F = 72\%\); \(p\) 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).

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
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 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

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**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 (RESCUE-Japan). 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. DWI-ASPECTS is analogous but certainly not identical to standard ASPECTS. 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. 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%). 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 reversed: 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. 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. 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 exactly to volumes 100–275 ml in a recent study. 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. 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. 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. The impact of imaging modality used to measure ASPECTS on clinical outcomes is elegantly illustrated by the study by Kaesmacher et al., 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{versus} 3–5 \textit{versus} 6–10), the rate of agreement rose to 66%, still far from perfect.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textless 6.\textsuperscript{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 \textit{versus} poor outcomes after EVT than a favorable CT.\textsuperscript{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 \textgreater 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.\textsuperscript{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 \textgreater 1.7. No difference in sICH rates was documented between the two groups. Fluid-attenuated inversion recovery vascular hyperintensities,\textsuperscript{38} apparent Diffusion Coefficient Gradient Within Diffusion Lesions,\textsuperscript{72} and incorporation of infarct location information on scoring\textsuperscript{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.\textsuperscript{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.\textsuperscript{75} In addition, there are contradictory observations
regarding safety from the only RCT specifically recruiting large core patients\textsuperscript{33} and the largest clinical registry that used propensity score matching.\textsuperscript{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.\textsuperscript{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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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. CRD4202234417).

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Supplemental material

Supplemental material for this article is available online.

References

1. Tsivgoulis G, Safouris A, Krogias C, et al. Endovascular reperfusion therapies for acute ischemic stroke: dissecting the evidence. Expert Rev Neurother 2016; 16: 527–534.
2. Tsivgoulis G, Kargiotis O, De Marchis G, et al. Off-label use of intravenous thrombolysis for acute ischemic stroke: a critical appraisal of randomized and real-world evidence. Ther Adv Neurol Disord 2021; 14: 997368.
3. Vogt G, Laage R, Shuaib A, et al. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: an analysis of the Virtual International Stroke Trials Archive (VISTA) database. Stroke 2012; 43: 1266–1272.
4. Von Kummer R, Allen KL, Holle R, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology 1997; 205: 327–333.
5. 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–e110.
6. European Medicines Agency website, https://www.ema.europa.eu/en/medicines/human/referrals/actilyse#all-documents-section (accessed 4 April 2022).
7. IST-3 Collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. Lancet Neurology 2015; 14: 485–496.
8. Dzialowski I, Hill MD, Coutts SB, et al. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. Stroke 2006; 37: 973–978.
9. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J 2021; 6: I–LXII.
10. Turk G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO): European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J 2019; 4: 6–12.
11. Barber PA, Demchuk AM, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy: ASPECTS Study Group – Alberta Stroke Programme Early CT Score. Lancet 2000; 355: 1670–1674.
12. Modi J, Menon B and Goyal M. Alberta Stroke Program Early CT Score (ASPECTS), http://www.ASPECTSsinStroke.Com
13. 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: 1723–1731.
14. Sarraj A, Grotta JC, Pujara DK, et al. Triage imaging and outcome measures for large core stroke thrombectomy: a systematic review and meta-analysis. J Neurointerv Surg 2020; 12: 1172–1179.
15. Diestro JDB, Dmytriw AA, Broocks G, et al. Endovascular thrombectomy for low ASPECTS large vessel occlusion ischemic stroke: a systematic review and meta-analysis. Can J Neurol Sci 2020; 47: 612–619.
16. Cagnazzo F, Derraz I, Dargazanli C, et al. Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS \(<6$: a meta-analysis. *J Neurointerv Surg* 2020; 12: 350–355.

17. Kerleroux B, Janot K, Hak JF, et al. Mechanical thrombectomy in patients with a large ischemic volume at presentation: systematic review and meta-analysis. *J Stroke* 2021; 23: 358–366.

18. Jiang Q, Wang H, Ge J, et al. Mechanical thrombectomy versus medical care alone in large ischemic core: an up-to-date meta-analysis. *Interv Neuroradiol* 2022; 28: 104–114.

19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009; 3: e123–130.

20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting – Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.

21. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: 14898.

22. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for including randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358: j4008.

23. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919.

24. DerSimonian R and Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; 45: 139–145.

25. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.

26. Deeks JJ, Higgins JP and Altman DG. Analysing data and undertaking meta-analyses. In: *Cochrane handbook for systematic reviews of interventions* (Version 6.3, updated February 2022). Cochrane, 2022, https://training.cochrane.org/handbook/current/chapter-10 (accessed 2 June 2022).

27. Atal I, Porcher R, Boutron I, et al. Fragility Index of meta-analyses, https://clinicalepidemiom.fr/fragility_ma/ (accessed 4 June 2022).

28. Mun KT, Bonomo JB, Liebeskind DS, et al. Fragility index meta-analysis of randomized controlled trials shows highly robust evidential strength for benefit of \(<3$ hour intravenous alteplase. *Stroke* 2022; 53: 2069–2074.

29. Wallace BC, Dahabreh IJ, Trikalinos TA, et al. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw* 2012; 49: 1–15.

30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1–48.

31. Román LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol* 2018; 17: 895–904.

32. Hill MD, Demchuk AM, Goyal M, et al. Alberta Stroke Program early computed tomography score to select patients for endovascular treatment: Interventional Management of Stroke (IMS)-III Trial. *Stroke* 2014; 45: 444–449.

33. Yoshimura S, Sakai N, Yamagami H, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med* 2022; 386: 1303–1313.

34. Almallouhi E, Al Kasab S, Hubbard Z, et al. Outcomes of mechanical thrombectomy for patients with stroke presenting with low Alberta Stroke Program Early Computed Tomography Score in the early and extended window. *JAMA Netw Open* 2021; 4: e2137708.

35. Bouslama M, Barreira CM, Haussen DC, et al. Endovascular reperfusion outcomes in patients with a stroke and low ASPECTS is highly dependent on baseline infarct volumes. *J Neurointerv Surg* 2022; 14: 117–121.

36. Broocks G, Flottmann F, Schönfeld M, et al. Incomplete or failed thrombectomy in acute stroke patients with Alberta Stroke Program Early Computed Tomography Score 0–5: how harmful is trying? *Eur J Neurol* 2020; 27: 2031–2035.

37. Deguchi I, Dembo T, Yoshimura S, et al. Relationship between magnetic resonance angiography-diffusion-weighted imaging mismatch and clinical outcome in endovascular treatment for acute ischemic stroke: subgroup analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism: Japan Registry. *J Stroke Cerebrovasc Dis* 2014; 23: 1471–1476.

38. Derraz I, Ahmed R, Mourand I, et al. FLAIR vascular hyperintensities predict functional outcome after endovascular thrombectomy in patients with large ischemic cores. *Eur Radiol* 2022; 32: 6136–6144.
39. Inoue M, Olivot JM, Labreuche J, et al. Impact of diffusion-weighted imaging Alberta stroke program early computed tomography score on the success of endovascular reperfusion therapy. *Stroke* 2014; 45: 1992–1998.

40. Jia B, Ren Z, Mokin M, et al. Current status of endovascular treatment for acute large vessel occlusion in China: a real-world nationwide registry. *Stroke* 2021; 52: 1203–1212.

41. Kaesmacher J, Chaloulos-Iakovidis P, Panos L, et al. Mechanical thrombectomy in ischemic stroke patients with Alberta Stroke Program Early Computed Tomography Score 0–5. *Stroke* 2019; 50: 880–888.

42. Kakita H, Yoshimura S, Uchida K, et al. Impact of endovascular therapy in patients with large ischemic core: subanalysis of recovery by endovascular salvage for cerebral ultra-acute embolism Japan Registry 2. *Stroke* 2019; 50: 901–908.

43. Kim SK, Yoon W, Park MS, et al. Outcomes are not different between patients with intermediate and high DWI-ASPECTS after stent-retriever embolectomy for acute anterior circulation stroke. *Am J Neuroradiol* 2016; 37: 1080–1085.

44. Meyer L, Bechstein M, Bester M, et al. Thrombectomy in extensive stroke may not be beneficial and is associated with increased risk for hemorrhage. *Stroke* 2021; 52: 3109–3117.

45. Ospel J, Kappelhof M, Groot AE, et al. Combined effect of age and baseline Alberta stroke program early computed tomography score on post-thrombectomy clinical outcomes in the MR CLEAN Registry. *Stroke* 2020; 51: 3742–3745.

46. Panni P, Michelozzi C, Richard S, et al. Effect of workflow metrics on clinical outcomes of low diffusion-weighted imaging Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) patients subjected to mechanical thrombectomy. *J Neurointerv Surg* 2020; 12: 742–746.

47. Sarraj A, Hassan AE, Savitz S, et al. Outcomes of endovascular thrombectomy vs medical management alone in patients with large ischemic cores: a secondary analysis of the optimizing patient’s selection for endovascular treatment in acute ischemic stroke (SELECT) study. *JAMA Neurology* 2019; 76: 1147–1156.

48. Yoo AJ, Zaidat OO, Chaudhry ZA, et al. Impact of pretreatment noncontrast CT Alberta Stroke Program Early CT Score on clinical outcome after intra-arterial stroke therapy. *Stroke* 2014; 45: 746–751.

49. Zaidat OO, Liebeskind DS, Jadhav AP, et al. Impact of age and Alberta stroke program early computed tomography score 0 to 5 on mechanical thrombectomy outcomes: analysis from the STRATIS registry. *Stroke* 2021; 52: 2220–2228.

50. Jiang S, Peng Y, Jing CH, et al. Endovascular thrombectomy can be beneficial to acute ischemic stroke patients with large infarcts. *J Neurosurg*. Epub ahead of print 1 May 2018. DOI: 10.3171/2017.11.JNS171297.

51. Lei C, Zhou X, Chang X, et al. Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS $\leq 5$. *J Stroke Cerebrovasc Dis* 2021; 30: 105748.

52. Manceau PF, Soize S, Gawlitza M, et al. Is there a benefit of mechanical thrombectomy in patients with large stroke (DWI-ASPECTS $\leq 5$)? *Eur J Neurol* 2018; 25: 105–110.

53. Song K, Guan M, Li W, et al. Acute ischemic stroke patients with diffusion-weighted imaging- Alberta Stroke Program Early Computed Tomography Score $\leq 5$ can benefit from endovascular treatment: a single-center experience and literature review. *Neuroradiology* 2019; 61: 451–459.

54. Xing PF, Zhang YW, Zhang L, et al. Higher baseline cortical score predicts good outcome in patients with low Alberta stroke program early computed tomography score treated with endovascular treatment. *Neurosurgery* 2021; 88: 612–618.

55. Schröder J and Thomalla G. A Critical review of Alberta stroke program early CT score for evaluation of acute stroke imaging. *Front Neurol* 2017; 7: 245.

56. Nezu T, Koga M, Nakagawara J, et al. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. *Stroke* 2011; 42: 2196–2200.

57. Hui FK, Obuchowski NA, John S, et al. ASPECTS discrepancies between CT and MR imaging: analysis and implications for triage protocols in acute ischemic stroke. *J Neurointerv Surg* 2017; 9: 240–243.

58. Lin K, Lee SA and Zink WE. What ASPECTS value best predicts the 100-mL threshold on diffusion weighted imaging? Study of 150 patients with middle cerebral artery stroke. *J Neuroimaging* 2011; 21: 229–231.
59. de Margerie-Mellon C, Turc G, Tisserand M, et al. Can DWI-ASPECTS substitute for lesion volume in acute stroke. *Stroke* 2013; 44: 3565–3567.

60. Yoshimoto T, Inoue M, Yamagami H, et al. Use of diffusion-weighted imaging-Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) and ischemic core volume to determine the malignant profile in acute stroke. *J Am Heart Assoc* 2019; 8: e012558.

61. Panni P, Lapergue B, Maïer B, et al. Clinical impact and predictors of diffusion weighted imaging (DWI) reversal in stroke patients with diffusion weighted imaging Alberta stroke program early CT score 0-5 treated by thrombectomy: diffusion weighted imaging reversal in large volume stroke. *Clin Neuroradiol*. Epub ahead of print 12 April 2022. DOI: 10.1007/s00062-022-01156-z.

62. Yamamoto N, Izumi Y, Yamamoto Y, et al. Factors associated with DWI-ASPECTS score in patients with acute ischemic stroke due to cerebral large vessel occlusion. *Clin Neurol Neurosurg* 2020; 199: 106316.

63. McTaggart RA, Jovin TG, Lansberg MG, et al. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography and MRI: reader agreement, modality agreement, and outcome prediction. *Stroke* 2015; 46: 407–412.

64. Van Seeters T, Biessels GJ, Niesten JM, et al. Reliability of visual assessment of non-contrast CT, CT angiography source images and CT perfusion in patients with suspected ischemic stroke. *PLoS ONE* 2013; 8: e75615.

65. Bendszus M, Bonekamp S, Berge E, et al. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke* 2019; 14: 87–93.

66. Van Horn N, Kniep H, Broocks G, et al. ASPECTS interobserver agreement of 100 investigators from the TENSION study. *Clin Neuroradiol* 2021; 31: 1093–1100.

67. Berkhemer OA, Jansen IG, Beumer D, et al. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. *Stroke* 2016; 47: 768–776.

68. Tan BY, Wan-Yee K, Paliwal P, et al. Good intracranial collaterals trump poor ASPECTS (Alberta Stroke Program Early CT Score) for intravenous thrombolysis in anterior circulation acute ischemic stroke. *Stroke* 2016; 47: 2292–2298.

69. Broocks G, Kniep H, Schramm P, et al. Patients with low Alberta Stroke Program Early CT Score (ASPECTS) but good collaterals benefit from endovascular recanalization. *J Neurointerv Surg* 2020; 12: 747–752.

70. McDonough R, Elsayed S, Faizy TD, et al. Computed tomography-based triage of extensive baseline infarction: ASPECTS and collaterals versus perfusion imaging for outcome prediction. *J Neurointerv Surg* 2021; 13: 869–874.

71. Kerleroux B, Janot K, Dargazanli C, et al. Perfusion imaging to select patients with large ischemic core for mechanical thrombectomy. *J Stroke* 2020; 22: 225–233.

72. Gwak DS, Choi W, Shim DH, et al. Role of apparent diffusion coefficient gradient within diffusion lesions in outcomes of large stroke after thrombectomy. *Stroke* 2022; 53: 921–929.

73. Tolhuisen ML, Ernst M, Boers AMM, et al. Value of infarct location in the prediction of functional outcome in patients with an anterior large vessel occlusion: results from the HERMES study. *Neuroradiology* 2022; 64: 521–530.

74. Œuvres II (1942), Paul Valéry, éd. Gallimard, coll. « Bibliothèque de la Pléiade », 1960, p. 864

75. Montalvo M, Mistry E, Chang AD, et al. Predicting symptomatic intracranial haemorrhage after mechanical thrombectomy: the TAG score. *J Neurol Neurosurg Psychiatry* 2019; 90: 1370–1374.

76. Broocks G, Hanning U, Flottmann F, et al. Clinical benefit of thrombectomy in stroke patients with low ASPECTS is mediated by oedema reduction. *Brain* 2019; 142: 1399–1407.