Stroke

ORIGINAL CONTRIBUTION

Endovascular Thrombectomy Versus Best Medical Therapy for Large Vessel Occlusion Stroke Beyond 24 Hours: A Systematic Review and Meta-Analysis

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BACKGROUND: The benefit of endovascular thrombectomy (EVT) beyond 24 hours from last known well in acute ischemic stroke remains uncertain. Although some slow progressors may retain salvageable tissue, supporting evidence in this ultra-late window comes mainly from small observational studies.

METHODS: We systematically searched PubMed, Embase, Scopus, Web of Science, and Cochrane Central up to February 2025 for studies comparing EVT and best medical therapy in patients with acute ischemic stroke treated >24 hours from last known well. Eligible studies reported functional independence (90-day 0–2 modified Rankin Scale score), excellent clinical outcome (90-day 0–1 modified Rankin Scale score), symptomatic intracranial hemorrhage, or 90-day mortality. Pooled unadjusted and adjusted odds ratios (ORs) with 95% CIs were calculated using random-effects meta-analyses. Subgroup analyses were performed by study design, stroke severity, imaging modality, and occlusion territory. Statistical heterogeneity was assessed using the I^2 statistic and the Cochran Q test, and the certainty of evidence (CoE) was assessed using the Grading of Recommendation, Assessment, Development, and Evaluation approach.

RESULTS: Ten observational studies (3 prospective and 7 retrospective) comprising 1871 patients (EVT: 866; best medical therapy: 1009) were included. EVT was associated with significantly higher odds of functional independence (8 studies; adjusted OR, 4.62 [95% CI, 3.30–6.47]; I^2=0%; low CoE) and excellent clinical outcome (2 studies; adjusted OR, 5.68 [95% CI, 2.49–12.97]; I^2=0%; very-low CoE). EVT increased the risk of symptomatic intracranial hemorrhage (4 studies; adjusted OR, 9.54 [95% CI, 3.78–21.07]; I^2=0%; low CoE), but 90-day mortality did not differ significantly between groups (4 studies; adjusted OR, 0.63 [95% CI, 0.30–1.31]; I^2=41.2%; very-low CoE). All subgroup analyses aligned with the main findings.

CONCLUSIONS: Our results revealed that EVT was associated with improved functional outcomes without an increase in 90-day mortality, despite a higher symptomatic intracranial hemorrhage risk. Given the limited CoE and overall study quality, ongoing randomized trials are essential to confirm these findings and guide patient selection in the ultra-late time window.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: intracranial hemorrhage ■ ischemic stroke ■ mortality ■ thrombectomy ■ tomography

Landmark randomized trials established the efficacy of endovascular thrombectomy (EVT) for patients with large vessel occlusion–acute ischemic stroke (LVO-AIS) and small infarct cores presenting within the early time window.[1–5] Since then, subsequent studies have progressively expanded EVT indications to the

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
AURORA	Analysis of Pooled Data from Randomized Studies of Thrombectomy More Than 6 hours After Last Known Well
BMT	best medical therapy
CTP	computed tomography perfusion
EVT	endovascular thrombectomy
LKW	last known well
LVO-AIS	large vessel occlusion–acute ischemic stroke
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
RCT	randomized clinical trial
sICH	symptomatic intracranial hemorrhage

late window[6] and to patients with large ischemic core,[7–11] demonstrating that selected patients can still achieve favorable outcomes beyond traditional criteria. Nevertheless, evidence supporting EVT for patients with a known last known well (LKW) time and presenting in the ultra-late window beyond 24 hours remains limited.

Several studies suggest that salvageable penumbra may persist beyond 24 hours, particularly in slow progressors with a small infarct core and robust collateral circulation.[12,13] This supports the hypothesis that EVT may remain beneficial in select patients with favorable imaging profiles, even beyond 24 hours from LKW. Notably, the AURORA (Analysis of Pooled Data From Randomized Studies of Thrombectomy More Than 6 hours After Last Known Well) meta-analysis reported a small median initial infarct volume among patients treated between 6 and 24 hours, implying that a substantial proportion had robust collateral circulation capable of limiting infarct growth over time.[6] Moreover, a differential treatment effect was observed, with a stronger association between EVT and favorable outcomes in patients treated between 12 and 24 hours compared with those treated in the 6- to 12-hour window. This reinforces the concept that late-presenting patients with small cores likely represent a very slow progressor phenotype, in whom infarct growth is significantly attenuated.

Data on EVT in the ultra-late window beyond 24 hours is derived exclusively from observational studies with modest sample sizes. A recent aggregate meta-analysis of proportions suggested that a considerable fraction of patients treated with EVT in this window can achieve favorable outcomes; however, it lacked a comparative arm and did not evaluate outcomes relative to best medical therapy (BMT).[14]

Whether EVT improves clinical outcomes compared with BMT in patients with AIS presenting beyond 24 hours from LKW remains unknown. Here, we conducted a systematic literature review and meta-analysis comparing the efficacy and safety outcomes of EVT versus BMT in patients with AIS presenting beyond 24 hours from stroke onset. We further performed predefined subgroup analyses to assess whether the observed treatment effects were consistent across different occlusion territories, imaging modalities, and stroke severity levels.

PATIENTS AND METHODS

Protocol, Guidance, and Data Availability

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline.[15] The study protocol and methods were registered with PROSPERO a priori (URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD420250652081).

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

Search Strategy and Eligibility Criteria

A systematic literature search was conducted by a medical librarian (C.M.M) across multiple databases, including the Ovid Embase, PubMed, Scopus, Web of Science, and Cochrane Central Library. The search aimed to identify relevant articles published from the earliest records available in each database up to February 2025. Search algorithms were tailored to the specifications of each database. Further details of the complete search strategy are provided in Table S1.

Nonrandomized studies (including open-label trials, real-world cohort studies, or case series) comparing the safety and efficacy of primary EVT with BMT versus BMT alone were included. No randomized controlled trials were identified. Eligible studies focused on adult patients (≥18 years) with anterior or posterior circulation AIS presenting more than 24 hours after symptom onset or LKW, and included at least 10 patients. Exclusion criteria included review articles, abstracts, editorials, letters, animal studies, and case reports. Table S2 provides a more detailed representation of patient-level inclusion and exclusion criteria.

Study Selection and Data Collection Process

The search strategy was systematically implemented across all databases. Retrieved records were first processed using EndNote X9, where duplicate entries were identified and removed. The remaining records were then

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exported in .XML format to Mendeley for further organization. Mendeley was used to convert the data into RIS format, allowing for expert review through the Rayyan platform (https://www.rayyan.ai/). Duplicate articles were carefully removed, and an initial screening of titles and abstracts was conducted by 4 independent reviewers (N.B., S.S., M.I.V.S., P.B.R.) based on predefined inclusion criteria to identify relevant studies. Discrepancies among reviewers were initially resolved through discussion, with a fifth reviewer (A.R.C.) serving as an arbitrator in cases where consensus could not be reached.

The following data were extracted from studies that were selected: first author, journal, publication date, study type, number of patients, number of EVT and BMT patients, age, female sex, baseline modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), ischemic core volume, Alberta Stroke Program Early Computed Tomography Score score, intravenous thrombolysis treatment, imaging modality, site of vascular occlusion, time window from the stroke onset to beginning of the intervention, intervention description, modified Treatment in Cerebral Infarction 2b-3, the statistical methods used for multivariable adjustments, and the prioritized outcomes.

Outcomes and Prioritization

The primary effectiveness outcome was the proportion of patients achieving functional independence at 90 days, defined by an mRS score of 0 to 2. The mRS is a 7-point ordinal scale (0=no symptoms; 6=death) that measures poststroke disability, with scores of 0 to 2 indicating independence in activities of daily living.[16] Secondary effectiveness outcomes included excellent clinical outcomes (90-day mRS score of 0–1). Safety outcomes included the incidence of symptomatic intracranial hemorrhage (sICH), as defined by each study, and all-cause mortality at 90 days.

Risk of Bias and Certainty of Evidence

The quality of the studies included in this analysis was evaluated based on the guidelines outlined in the Cochrane reviewers' handbook.[17] For the methodological assessment of nonrandomized studies, 2 independent reviewers (M.I.V.-S. and F.A.C.-E.) utilized the Risk of Bias in Nonrandomized Studies of Interventions tool.[18]

To evaluate the certainty of the evidence derived from the eligible studies, a quantitative synthesis was conducted following the Cochrane recommendations.[17] The grading of recommendation, assessment, development, and evaluation approach was used.

Data Synthesis

A meta-analysis was conducted when at least 2 studies reported the same effect estimate for a specific outcome. For the meta-analysis, we computed pooled unadjusted odds ratios (ORs) with their 95% CIs for all outcomes using a random-effects model with the Restricted Maximum Likelihood (REML) method. Subsequently, the adjusted ORs reported in each study were pooled using a random-effects model. When zero events or zero CIs were reported in a study, a continuity correction was applied to enable analysis of those studies.[19] We utilized the Cochran Q and I^2 tests to evaluate statistical heterogeneity. An I^2 statistic with values of >25%, >50%, and >75% indicated low, considerable, and substantial levels of heterogeneity, respectively.[20]

To explore potential sources of heterogeneity among study results, we performed subgroup analyses according to (1) study design (prospective versus retrospective), (2) occlusion territory (studies including an exclusively anterior circulation LVO population versus others), (3) imaging modality used (advanced imaging, including computed tomography perfusion or magnetic resonance imaging, versus nonadvanced imaging), (4) stroke severity (low NIHSS score <10 versus high NIHSS score ≥10), (5) geography (US-based and China-based studies), and (6) quality scores (serious versus moderate risk of bias, according to the Risk of Bias in Nonrandomized Studies of Interventions tool. Subgroup analyses were conducted when at least 2 studies were available in each comparison group; otherwise, sensitivity analyses were performed. All analyses and plots were generated using R statistical software (version 4.2.0) and R Studio.

RESULTS

Study Selection and Characteristics

The search yielded a total of 4783 documents, after which 173 duplicates were removed (Figure S1). After the removal of duplicates, the titles and abstracts of 4610 articles were screened for relevance, after which 60 potentially eligible documents remained. In the full-text evaluation, 50 articles were excluded (Table S3). Finally, 10 studies were included in the analysis. All had a nonrandomized design.

A total of 1871 patients were included, with 866 patients (46.3%) undergoing EVT, and 1009 (53.9%) receiving BMT. Seven studies were single-center,[21–27] and 3 were multicenter.[28–30] Three studies were prospective,[22,25,28] whereas the rest were retrospective. Patient characteristics, including age, sex, baseline NIHSS or Alberta Stroke Program Early Computed Tomography Score, and use of intravenous thrombolysis treatment, are detailed in the Tables S4 and S5. Briefly, the median age ranged from 61.6 to 69.5 in the EVT group, and 61 to 78.3 in the BMT group, with females comprising 40.6% of the cohort. All studies reported baseline NIHSS scores, ranging from 2 to 17 in EVT and 3–21.5 in BMT. Among the included studies, 1 specifically enrolled patients with

mild stroke (NIHSS score <5),[23] 4 explicitly excluded patients with mild stroke,[22,24,25,27] and the remaining 5 had no NIHSS-based inclusion criteria. The ischemic core volume was reported in 5 studies,[22,25,27,28,30] with median values of 0 to 11 mL (EVT) and 0 to 13.4 mL (BMT). The median Alberta Stroke Program Early Computed Tomography Score ranged from 7 to 9 in EVT and 5 to 9 in BMT, as reported in 8 studies.[21–25,28–30] Intravenous thrombolysis treatment, reported in 6 studies,[21,22,24,25,28,30] was 7.2% in both groups. The highest intravenous thrombolysis treatment rate was reported by Dhillon et al[24] in the EVT group, being 15.7%. Occlusions were most common in M1(41.4%), ICA (31.5%), and M2 (9.5%) in EVT, whereas BMT had ICA (30.9%), M1 (30.2%), and M2 (6.7%) occlusions. Chen et al[21] and Mohamed et al[29] included a combined population of patients with anterior and posterior circulation stroke, whereas the rest of the studies included exclusively anterior circulation stroke. The median time from LKW ranged from 27.1 to 96 hours in the EVT group and 22.7 to 77 hours in the BMT group. Successful reperfusion (modified Treatment in Cerebral Infarction 2b–3) was achieved in 75.2%.[22–26,28–30]

Risk of Bias and Certainty of Evidence

We assessed the quality of 10 nonrandomized studies. Six were judged to have a serious overall risk of bias,[22,23,25–27,29] as detailed in Figure S2. Eight studies used statistical adjustments to mitigate confounding,[21,22,24,25,27–30] of which 3 were prospective. Detailed descriptions of the statistical methods used in each study can be found in Table S6. The majority (70%) were retrospective, raising concerns about selection bias. Confounding was not adequately addressed in 2 studies,[23,26] and only 1 study implemented blinding during data collection.[27] Two studies had a serious risk of bias related to missing data, as participants were excluded during follow-up.[26,29] Outcome measurement bias was considered critical in all but one study (Dhillon et al[24]), which incorporated blinded assessment.[24] In addition, all studies demonstrated a moderate risk of bias in the selection of reported results, primarily due to ambiguity in outcome definitions or subgroup reporting. The overall certainty of the evidence for each outcome and its details is shown in Table 1 and Table S7.

Functional Independence

Seven studies (EVT: 686 patients; BMT: 545 patients) reported unadjusted outcomes for functional independence. In the pooled unadjusted analysis, 43.3% of patients treated with EVT achieved functional independence compared with 29.5% in the BMT group (OR, 2.25 [95% CI, 1.17–4.32]; I^2=81.7%). Subgroup analysis by study design showed a significant association in prospective studies (OR, 2.50 [95% CI, 1.64–3.82]; I^2=10%), whereas no significant association was found in retrospective studies (OR, 2.17 [95% CI, 0.73–6.43]; I^2=89.2%). However, the test for subgroup differences was not statistically significant (P=0.809; Figure 1A).

Eight studies reported adjusted outcomes. In the adjusted meta-analysis, EVT was significantly associated with higher odds of functional independence (adjusted OR [aOR], 4.62 [95% CI, 3.30–6.47]; I^2=0%). A similar strength of association was observed in both retrospective studies (aOR, 5.47 [95% CI 3.30–9.06]) compared with prospective studies (aOR, 4.04 [95% CI 2.57–6.34]; Figure 1B).

Excellent Clinical Outcome

Six studies (EVT: 524 patients; BMT: 434 patients) reported unadjusted excellent clinical outcomes. In the unadjusted analysis, the rate of excellent clinical outcome was higher in the EVT group (32%) compared with BMT (13.3%), with a pooled unadjusted OR of 3.26 ([95% CI, 2.28–4.65]; I^2=0%; Figure 1C).

Two studies (EVT: 135 patients; BMT: 150 patients) reported adjusted excellent clinical outcomes. In the adjusted meta-analysis, EVT was associated with higher odds of an excellent clinical outcome (aOR, 5.68 [95% CI, 2.49–12.97]; I^2=0%; Figure 1D).

Symptomatic Intracranial Hemorrhage

Unadjusted sICH (EVT: 756 patients; BMT: 593 patients) outcomes were reported in 8 studies. EVT

Table 1. Summary of Safety and Efficacy Outcomes Comparing EVT Versus BMT in Patients Presenting >24 Hours After Stroke Onset

Outcome	Pooled rate		Unadjusted meta-analysis			Adjusted meta-analysis			
	EVT	BMT	No. of studies	Pooled OR (95% CI)	I^2	No of studies	Pooled aOR (95% CI)	I^2	Grade*
Functional independence	43.3%	29.5%	7	2.25 (1.17–4.32)	81.7%	8	4.62 (3.30–6.47)	0%	⨁⨁◯◯: low
Excellent clinical outcome	35%	13.3%	6	3.26 (2.28–4.65)	0%	2	5.68 (2.49–12.97)	0%	⨁◯◯◯: very low
sICH	6%	1.1%	8	3.77 (1.71–8.32)	0%	4	9.54 (3.78–24.07)	0%	⨁⨁◯◯: low
90-d mortality	21%	21.8%	7	0.75 (0.50–1.13)	15.4%	4	0.63 (0.30–1.31)	41.2%	⨁◯◯◯: very low

aOR indicates adjusted odds ratio; BMT, best medical therapy; EVT, endovascular thrombectomy; OR, odds ratio; and sICH, symptomatic intracranial haemorrhage.
*⨁◯◯◯: very low; ⨁⨁◯◯: low; ⨁⨁⨁◯: moderate; and ⨁⨁⨁⨁: high.

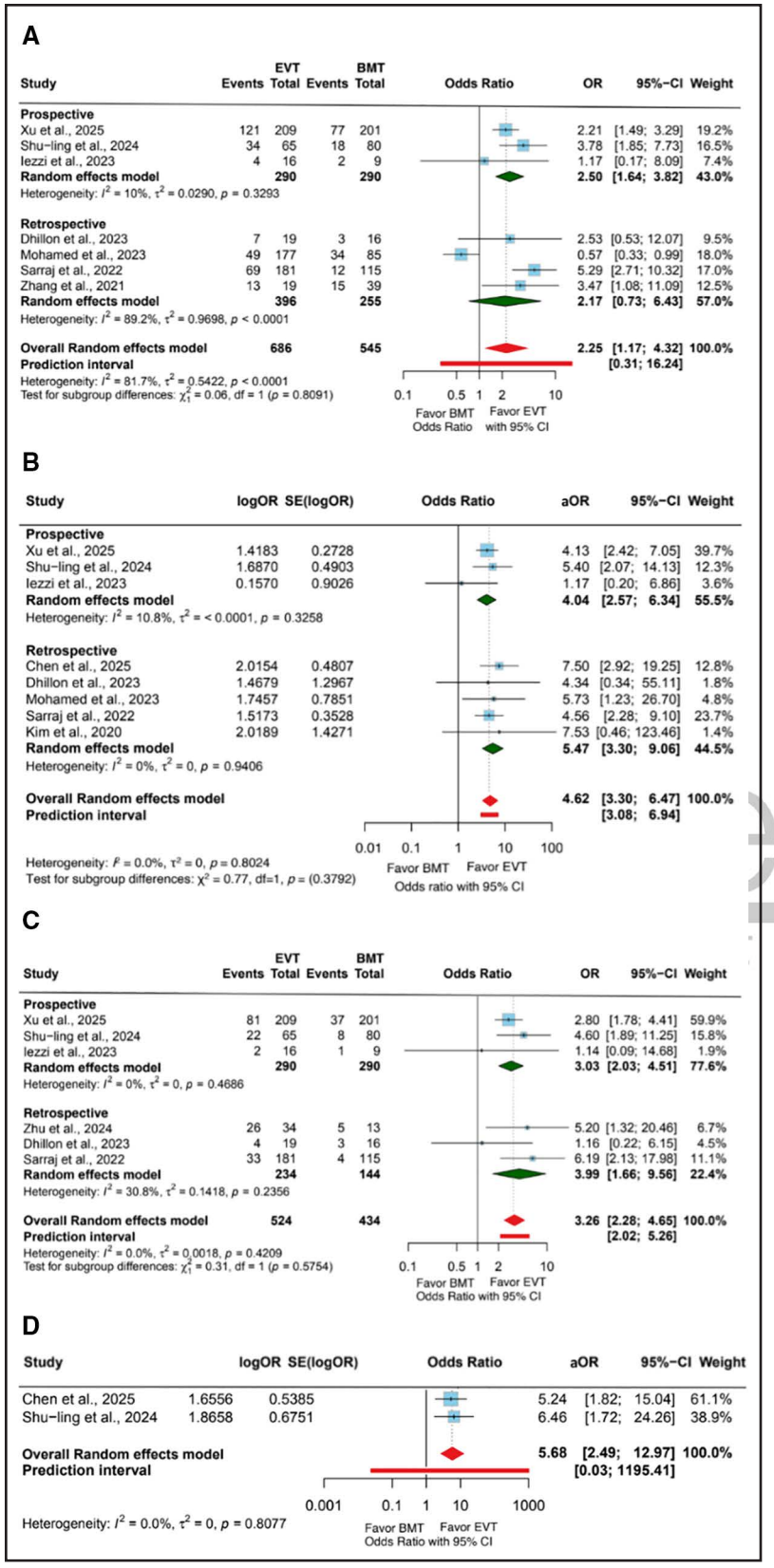

Figure 1. xxx.
Forest plots for (**A**) unadjusted functional independence, (**B**) adjusted functional independence, (**C**) unadjusted excellent clinical outcome, and (**D**) adjusted excellent clinical outcome. aOR indicates adjusted odds ratio; BMT, best medical therapy; EVT, endovascular thrombectomy; and OR, odds ratio.

was associated with a higher risk of sICH compared with BMT (6% versus 1.1%; OR, 3.77 [95% CI, 1.71–8.32]; I²=0%). Subgroup analysis showed a significant association in retrospective studies (OR, 3.47 [95% CI, 1.37–8.80]; I²=0%), whereas no significant difference was found in prospective studies (OR, 3.91 [95% CI,

0.56–27.15]; I^2=34.7%). However, the test for subgroup differences was not statistically significant (P=0.914; Figure 2A).

Adjusted outcomes were reported in 4 studies. EVT was associated with significantly higher odds of sICH (aOR, 9.54 [95% CI, 3.78–24.07]; I^2=0%; Figure 2B).

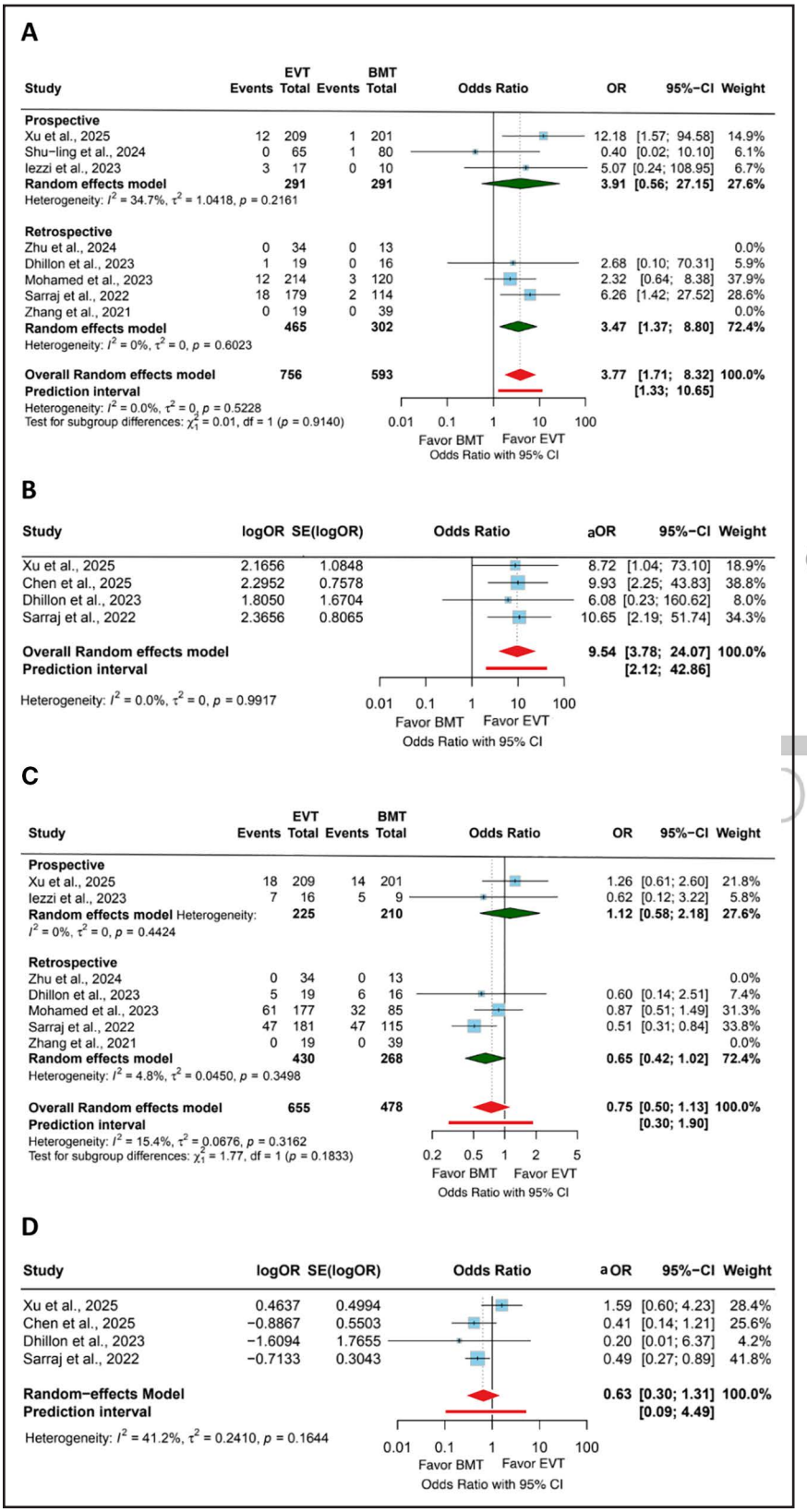

Figure 2. xxx.
Forest plots for (**A**) unadjusted symptomatic intracranial hemorrhage (sICH), (**B**) adjusted sICH, (**C**) unadjusted 90-day mortality, and (**D**) adjusted 90-day mortality outcomes. aOR indicates adjusted odds ratio; BMT, best medical therapy; EVT, endovascular thrombectomy; and OR, odds ratio.

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90-Day Mortality

Seven studies (EVT: 655 patients; BMT: 478 patients) reported unadjusted 90-day mortality outcomes. 90-day mortality rates were similar between groups (EVT: 21% versus BMT: 21.8%; OR, 0.75 [95% CI, 0.50–1.13]; I^2=15.4%). Subgroup analysis showed no significant association in either retrospective (OR, 0.65 [95% CI, 0.42–1.02]; I^2=4.8%) or prospective studies (OR, 1.12 [95% CI, 0.58–2.18]; I^2=0%; Figure 2C).

Adjusted 90-day mortality outcomes were reported in 4 studies. Odds of 90-day mortality were not significantly different between EVT and BMT (aOR, 0.63 [95% CI, 0.30–1.31]; I^2=41.2%; Figure 2D).

Subgroups and Sensitivity Analyses

Meta-analyses of subgroups based on occlusion territory, use of advanced imaging, and stroke severity are presented in Table 2. EVT was significantly associated with higher odds of functional independence across all subgroups. Similarly, EVT was associated with significantly higher odds of sICH in each subgroup. Regarding 90-day mortality, results in the anterior circulation, advanced imaging, and low NIHSS score (<10) subgroups were consistent with the main analysis, showing no significant interactions between treatment choice (EVT and BMT) and outcomes. Notably, EVT was associated with reduced 90-day mortality in the high NIHSS subgroup; however, the test for subgroup differences was not statistically significant (P=0.458).

Finally, sensitivity analyses were performed to account for potential population overlaps (Table S8). The results remained consistent with the main findings after sequential exclusion of each potentially overlapping study.

DISCUSSION

In this systematic review and meta-analysis, we found that EVT was significantly associated with improved functional outcomes in patients with AIS presenting beyond 24 hours from stroke onset. Specifically, EVT led to higher odds of achieving both functional independence (90-day 0–2 mRS) and excellent clinical outcome (90-day 0–1 mRS) compared with BMT. These benefits were observed despite a higher risk of sICH in the EVT group. Notably, 90-day mortality rates did not differ significantly between the 2 treatment strategies. Subgroup analyses based on occlusion territory, imaging modality, and stroke severity were consistent with the overall findings.

The AURORA meta-analysis demonstrated the efficacy of EVT for anterior circulation stroke in select patients treated between 6 and 24 hours after LKW.[6] Our findings represent an important extension to this data, supporting

Table 2. Adjusted Meta-Analysis Stratified by Subgroups Based on Occlusion Territory, Use of Advanced Imaging, Stroke Severity, Geography, and Quality Scores

Outcome	Subgroup	No. of studies	Pooled aOR (95% CI)	I^2	P value*
Functional independence	Anterior circulation LVO	4	4 (2.67–6.01)	0%	0.216
	Other territory	4	6.33 (3.47–11.56)	0%	
	Advanced imaging	6	4.52 (3.15–6.50)	0%	0.761
	Nonadvanced imaging	2	5.26 (2.14–12.92)	0%	
	Low NIHSS score (<10)	2	4.88 (2.89–8.26)	14.3%	0.802
	High NIHSS score (≥10)	6	4.45 (2.73–7.26)	0%	
	US-based studies	3	4.05 (2.23–7.33)	9.1%	0.59
	China-based studies	4	4.94 (3.26–7.47)	0%	
	Serious RoB	4	4.35 (1.48–12.8)	0%	0.831
	Moderate RoB	4	4.70 (3.18–6.93)	0%	
Symptomatic intracranial hemorrhage	Anterior circulation LVO	3	9.30 (2.85–30.37)	0%	…
	Advanced imaging	3	9.92 (3.78–26.03)	0%	…
	Low NIHSS score (<10)	2	9.51 (2.82–32.15)	0%	0.994
	High NIHSS score (≥10)	2	9.58 (2.31–39.77)	0%	
	China-based studies	2	9.51 (2.82–32.15)	0%	…
90-d mortality	Anterior circulation LVO	3	0.73 (0.27–2.03)	55.7%	…
	Advanced imaging	3	0.67 (0.31–1.45)	57.5%	…
	Low NIHSS score (<10)	2	0.83 (0.22–3.10)	69.7%	0.458
	High NIHSS score (≥10)	2	0.48 (0.27–0.86)	0%	
	China-based studies	2	0.83 (0.22–3.10)	69.8%	…

aOR indicates adjusted odds ratio; LVO, large vessel occlusion; and NIHSS, National Institutes of Health Stroke Scale.
*Derived from tests for subgroup differences. Subgroup analyses were conducted when at least 2 studies were available in each comparison group; otherwise, sensitivity analyses were performed.

the notion that the beneficial effect of EVT may extend beyond 24-hour time window. Specifically, we observed that EVT was associated with higher odds of achieving functional independence and excellent clinical outcomes compared with BMT. Notably, the rates of functional independence (43.3%) and excellent outcome (35%) in the EVT arm of our study closely resemble those reported in AURORA (45.9% and 28.2%, respectively), reinforcing the consistency and promise of EVT even in ultra-late time windows, as these patients may exhibit a robust collateral support that mitigates infract growth beyond 24 hours.

The dynamic nature of infarct progression may explain why EVT remains beneficial in selected patients beyond traditional timeframes. Infarct growth is multifactorial and highly variable process, influenced by individual patient characteristics and regional brain differences. Several studies have shown that infarct growth has a logarithmic temporal pattern, with a rapid rate of expansion during the early hours after stroke onset and a slower growth rate in later phases.[31] Individuals with robust collateral circulation may preserve penumbral tissue far longer than traditional time-based cutoffs suggest, characterizing a slow progressor phenotype that may remain amenable to reperfusion.[31] In our study, the median infarct core volume among treated patients was <15 cm^3, despite the presence of severe neurological symptoms typically associated with LVO. This finding supports the notion that the majority of EVT cases performed in the ultra-late window are likely offered to slow progressors.

Variability in infarct growth among individuals is a critical determinant of EVT eligibility, and growing evidence suggests that infarct progression may be modifiable.[32] Emerging strategies such as the use of neuroprotective agents, collateral circulation augmentation, and therapeutic hypothermia have shown potential to slow infarct growth, offering opportunities to temporarily shift patients from a fast to a slow progressor phenotype.[33–35] These approaches may be particularly valuable in resource-limited settings, where access to timely EVT is often delayed. Furthermore, the molecular cascade of ischemic injury evolves over hours to days, and recanalization beyond 24 hours may still mitigate these mechanisms, potentially improving tissue viability and functional recovery.[36,37]

Our meta-analysis found an increased risk of sICH associated with EVT. Notably, the risk was substantially higher in the adjusted analysis (OR, 9.34) compared with the unadjusted analysis (OR, 3.77), suggesting a significant influence of confounding factors. Despite these findings, the pooled sICH rate in our study (6%) was comparable to that reported in the AURORA meta-analysis (5.3%).[6] In addition, 90-day mortality rates between EVT and BMT were not significantly different in our analysis. Although AURORA reported a mortality rate of 16.5%,[6] our meta-analysis found a rate of 21%. These findings suggest that, although EVT may carry an increased risk of sICH compared with BMT, it does not seem to translate into higher mortality and remains within the expected safety profile established by prior thrombectomy trials. Nevertheless, these findings highlight the critical role of meticulous patient selection and close procedural monitoring in minimizing hemorrhagic risks and optimizing the clinical benefit of EVT.

Several ongoing trials are currently investigating the efficacy of EVT beyond 24 hours from stroke onset (Table 3). These include studies focused on both anterior and posterior circulation strokes, underscoring the growing influence of recent positive EVT trials in posterior circulation on contemporary endovascular practice. Most of these ultra-late window trials, as well as the observational studies included in our meta-analysis (Table S5), use advanced neuroimaging modalities, such as CTP or magnetic resonance perfusion, to identify patients with favorable tissue profiles, following selection strategies similar to those used in late-window trials like DAWN and DEFUSE 3 (6–24 hours).[38] Interestingly, the DONE SYMPLE trial deviates from this trend by using noncontrast CT with artificial intelligence-based LVO detection and core infarct volume estimation for patient selection,[39] potentially providing important insight into whether simplified imaging approaches may suffice in this ultra-late window. This question remains particularly relevant given prior evidence suggesting comparable outcomes between patients selected with noncontrast CT alone and those selected with advanced neuroimaging (CTP or magnetic resonance perfusion) during the 6- to 24-hour window.[40–42] However, recent findings from the TRACK-LVO trial suggest that beyond 24 hours, EVT was associated with improved functional outcomes only among patients who met DAWN or DEFUSE 3 eligibility criteria, whereas no such benefit was observed in ineligible patients.[28] Future RCTs and individual patient-level meta-analyses may help delineate which subgroups of patients with stroke stand to benefit most from EVT in the ultra-late time window, while minimizing associated risks. These efforts may also clarify the role of advanced imaging in selecting appropriate candidates for treatment.

The findings of this systematic review should be interpreted in the context of some limitations. First, a substantial proportion of the included studies were rated as having moderate to serious risk of bias, which may affect the overall generalizability of the results. Second, the pooled data are subject to inherent biases associated with the retrospective and observational nature of the included studies. Although most studies reported adjusted analyses, enabling the estimation of pooled effect sizes, the potential influence of unmeasured confounding variables cannot be excluded. We observed inconsistent and often sparse covariate adjustments across studies, with varying types of covariates included in each analysis, largely reflecting differences in baseline characteristics between treatment arms. In addition, due to the nonrandomized design of these studies, treatment

Table 3. Ongoing Clinical Trials Evaluating EVT in Acute Ischemic Stroke Beyond 24 Hours

Trial name	Region	Inclusion criteria	Time window	Intervention	Primary outcomes	Status
SKIP-EXTEND (jRCT1032230344)	Japan	Adults with anterior circulation LVO; NIHSS score ≥6	24–72 h from LKW	EVT plus BMT vs BMT alone	90-d 0–2 mRS score	Ongoing
LATE-MT (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05326932)	China	Adults with anterior circulation LVO; evidence of salvageable brain tissue via imaging (CTP or MRP)	24–72 h from LKW	EVT plus BMT vs BMT alone	Shift (improvement) in scores on the 90-d mRS score	Ongoing
BAOCHE2 (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06560203)	China	Adults with acute BAO or intracranial segments of both vertebral arteries (V4); NIHSS score ≥6.	24–72 h from LKW	EVT plus BMT vs BMT alone	Good functional status (90-d 0–3 mRS score)	Ongoing
VBAO-LATE (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06510634)	China	Adults with acute VBAO	Beyond 24 h from LKW	EVT plus BMT vs BMT alone	90-d 0–3 mRS score	Ongoing
DONE SYMPLE	Global (United States, South America, Europe)	Adults with anterior circulation LVO; NIHSS score ≥8.	24–72 h from LKW	EVT plus BMT vs BMT alone	Shift (improvement) in scores on the 90-d mRS score	Ongoing
SELECT LATE	Global (North America, Europe, Australia)	Not specified	Beyond 24 h from LKW	EVT plus BMT vs BMT alone	Functional independence	Ongoing
URL: https://www.clinicaltrials.gov; Unique identifier: NCT06654375	China	Adults with anterior circulation LVO; NIHSS score ≥2.	24–72 h from LKW	EVT plus BMT vs BMT alone	Shift (improvement) in scores on the 90-d mRS score	Ongoing
TRACK-LVO Late (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06200753)	China	Patients with anterior circulation LVO	24–168 h from LKW	EVT plus BMT vs BMT alone	Functional independence at 90 d (mRS score, 0–2)	Completed

BAO indicates basilar artery occlusion; BMT, best medical therapy; CTP, computed tomography perfusion; EVT, endovascular thrombectomy; LKW, last known well; LVO, large vessel occlusion; MRP, magnetic resonance perfusion; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and VBAO, vertebrobasilar artery occlusion.

decisions regarding EVT versus BMT were made at the discretion of the treating team, which may have introduced selection bias. Moreover, limited information on control group characteristics makes it unclear whether these patients were eligible for EVT, which may have introduced additional treatment selection bias. Third, the inherent constraints of a study-level meta-analysis limited our ability to perform all prespecified subgroup analyses for each outcome. Fourth, variability in the definition of sICH across studies introduced clinical heterogeneity. However, the direction and magnitude of effect sizes for sICH were consistent across studies, all indicating a higher risk with EVT. In addition, statistical heterogeneity for sICH comparisons was low (I^2=0%), suggesting that definitional differences likely had a limited impact on the overall findings. Fifth, because each meta-analysis included ≤10 studies, we were unable to reliably assess publication bias using funnel plots, as their interpretability is limited in small sample sizes. Sixth, limited sample sizes restrict the precision of between-study variance (τ^2) estimation in random-effects models, potentially affecting heterogeneity adjustment and the width of CIs. Seventh, for outcomes with low event rates, pooled estimates may be vulnerable to type I error due to narrow CIs. Finally, for studies reporting zero events or CIs including zero, a continuity correction was applied, which may influence the pooled effect estimates.

CONCLUSIONS

In conclusion, this meta-analysis suggests that EVT could be effective and offer a favorable risk-benefit ratio in selected patients with AIS treated beyond 24 hours from symptom onset. EVT was associated with significantly higher odds of achieving functional independence and excellent clinical outcomes compared with BMT, despite an increased risk of sICH. Importantly, this elevated sICH risk did not translate into higher 90-day mortality. Although constrained by low certainty of evidence, these findings suggest that, with appropriate patient selection, EVT may be safely and effectively extended into the ultra-late time window. Ongoing RCTs will be essential to validate these findings, refine patient selection criteria, and determine the role of imaging modalities in guiding treatment decisions for this emerging clinical frontier.

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Supplemental Material

Supplemental Methods
Tables S1–S8
Figures S1–S2

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