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Review

Endovascular Thrombectomy for Large Ischemic Strokes: A Living Systematic Review and Meta-Analysis of Randomized Trials

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Background and Purpose New studies have shown that endovascular thrombectomy (EVT) is safe and effective for acute ischemic stroke (AIS) patients with large ischemic areas. The aim of our study is to conduct a living systematic review and meta-analysis of randomized trials comparing EVT versus medical management only.

Methods We searched MEDLINE, Embase, and the Cochrane Library to identify randomized controlled trials (RCTs) comparing EVT versus medical management alone in AIS patients with large ischemic regions. We conducted our meta-analysis using fixed-effect models to compare functional independence, mortality, and symptomatic intracranial hemorrhage (sICH) between EVT and standard medical management only. We assessed the risk of bias using the Cochrane risk-of-bias tool and the certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluations approach.

Results Of 14,513 citations, we included 3 RCTs with a total of 1,010 participants. We found low-certainty evidence of possibly a large increase in the proportion of patients with functional independence (risk difference [RD] 30.3%, 95% CI 15.0% to 52.3%), low-certainty evidence of possibly a small non-significant decrease in mortality (RD -0.7%, 95% CI -3.8% to 3.5%), and low-certainty evidence of possibly a small non-significant increase in sICH (RD 3.1%, 95% CI -0.3% to 9.8%) for AIS patients with large infarcts who underwent EVT compared to medical management only.

Conclusion Low-certainty evidence shows that there is possibly a large increase in functional independence, a small non-significant decrease in mortality, and a small non-significant increase in sICH amongst AIS patients with large infarcts undergoing EVT compared to medical management only.

Keywords Thrombectomy; Large infarct; Low ASPECTS; Systematic review; GRADE

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Introduction

Endovascular thrombectomy (EVT) is now the gold standard treatment modality for acute ischemic stroke (AIS) caused by large vessel occlusion (LVO).[1] The current guidelines for AIS management state that only patients with an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≥6 are eligible for EVT.[1,2] Although AIS patients with large ischemic region on neuroimaging represent a considerable proportion of LVO strokes (around 20%), those patients were excluded or underrepresented in EVT trials due to the concern of bleeding from reperfusion.[3-6] However, 3 randomized clinical trials (RCT) were recently conducted to assess the efficacy of EVT versus standard medical care alone in AIS patients with large-sized ischemic regions in the initial neuroimaging studies.[7-9] Therefore, we conducted this timely living systematic review and meta-analysis to provide robust evidence on the efficacy and safety of EVT in AIS patients with large ischemic region.

Methods

Standardized reporting and registration

We adhered to Cochrane systematic review methodology and formatted the review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (Supplementary Table 1).[10,11] We prospectively registered the systematic review protocol on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023398742).

Data sources and searches

With the aid of an information specialist, we searched MEDLINE (through Ovid), Embase, and the Cochrane Library from inception to February 10, 2023. We did not use any language restrictions. The detailed search strategies are described in Supplementary Table 2. We also hand-searched the grey literature and the reference lists of included studies.

Study selection

We included records addressing the following eligibility criteria:

Population

We sought studies including adult patients aged 18 years or older presenting with AIS and are found to have a large ischemic area on baseline neuroimaging, defined as having an ASPECTS value of less than 6 regardless of imaging modality used or having an infarct core volume of at least 50 mL. We planned to evaluate different subgroups, including different core infarct sizes and imaging criteria. We excluded *in vitro*, animal, or post-mortem studies.

Intervention

We sought studies comparing EVT to standard medical management, regardless of time from onset to treatment. We also determined *a priori* to evaluate different types of endovascular procedures performed adjunctively to thrombectomy (e.g., stenting, angioplasty).

Outcomes

Outcomes of interest were the proportion of patients who achieved functional independence (defined as a modified Rankin Scale [mRS] score of 0 to 2, at 90 days); mortality as death at 90 days after stroke onset due to any cause; symptomatic intracranial hemorrhage (sICH) (defined as any intracranial hemorrhage associated with worsening neurologic exam, clinical deterioration, or death, adapted from the Heidelberg Bleeding Classification);[12] proportion of patients with an mRS of 0 to 3 at 90 days; improvement in any domain on the National Institutes of Health Stroke Scale (NIHSS) at 24 to 48 hours after randomization; and any intracranial hemorrhage.

Study designs

We included RCTs only given their high quality of evidence and for quantitative assessment. We excluded all other study designs, such as observational studies, editorials, commentaries, guidelines, literature reviews, systematic reviews and meta-analyses, conference abstracts, and news articles.

Screening

Reviewers participated in calibration exercises using piloted standardized screening forms prior to the screening process. Teams of two reviewers independently screened and verified each citation. Subsequently, we retrieved the full texts of those citations that were deemed potentially eligible. Each full text was screened by one reviewer and another reviewer verified its eligibility. A third reviewer resolved any disagreements when necessary.

Data collection

Reviewers extracted data from each eligible RCT independently into an Excel spreadsheet via Microsoft Excel 2021 and verified the extracted data in duplicate using previously developed standardized data abstraction forms. Reviewers extracted the following characteristics: study characteristics (e.g., country, study design), patient characteristics (e.g., sample size, age, sex, prior medical history, NIHSS score, vessel involved, tandem occlusion, stroke etiology), intervention and comparator details (e.g., intravenous thrombolytic agent), and management outcomes, including mRS scores, mortality, intracranial hemorrhage, and procedural complications.

Risk of bias assessment

Two reviewers independently assessed the quality of included trials in strict accordance using the revised Cochrane risk-of-bias tool (RoB 2) for randomized controlled trials.[13] We improved the reliability of RoB 2, especially low interrater reliability and complex terminology, by training the authors prior to implementation.[14] Any discrepancies between the two assessors were resolved through discussion and including a third assessor.

Data synthesis and analysis

We synthesized the data in narrative and tabular formats. We conducted meta-analysis using the Mantel-Haenszel method to calculate risk ratios (RRs) and the associated 95% confidence intervals (CIs), for all patient-important outcomes reported by more than one study. We used the crude event rate and the associated CIs to calculate the RRs for dichotomous outcomes. For computing risk differences (RDs) and 95% CIs, we applied the RRs to the baseline risks from a well-designed, high-quality multi-center prospective cohort study of 2,420 patients with acute large vessel occlusions.[15] When median and range values were reported, or when standard deviations (SDs) were not reported, we estimated the means and standard deviations used methods detailed in the Cochrane Handbook[10] and by Wan et al.[16] We synthesized our findings into funnel plots to assess for asymmetry for each outcome, and evaluated for statistical heterogeneity using inconsistency measures, Cochran's Q test and I^2. We planned to perform subgroup analysis if there were at least two studies reporting outcomes per subgroup, irrespective of heterogeneity. All statistical analyses were done by Stata/MP version 17 for Microsoft Windows (StataCorp, College Station, TX, USA).

Certainty of evidence assessment

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the certainty of evidence for each outcome (high, moderate, low, or very low), and developed GRADE evidence profiles using the GRADEpro app (www.gradepro.org).[17,18] We used the following standard terminology to describe the strength of comparison for each outcome: "there is" for high-certainty of evidence, "there probably is" for moderate-certainty of evidence, and "there possibly is" for low- or very low-certainty of evidence. We used previously derived minimally important different thresholds for functional independence, mortality, and sICH from a previously developed guideline panel strategy.[19]

Living review and literature surveillance

We will use our search strategies to perform monthly updates or alerts. If new evidence is available that is sufficient to change the overall assessment, certainty of evidence, and provide more information on additional outcomes, then we would meta-analyze these findings and report the results in an updated manuscript.

Results

Of 14,513 citations, we identified 16 potentially eligible studies and included 3 RCTs with a total of 1,010 participants (Figure 1). The summary of the 3 RCTs is found in the Graphical Overview for Evidence Reviews (GOfER) diagram (available at https://ibb.co/26FWhyK).

Characteristics of included studies

Table 1 describes the characteristics of the included RCTs reporting on outcomes for AIS patients with large ischemic regions who underwent EVT versus those who received medical management only.[7-9] The number of included patients ranged from 203 to 455,[7-9] two studies used alteplase at doses ranging from 0.6 to 0.9 mg/kg,[7,9] and one study used alteplase or tenecteplase at unspecified doses.[8] Moreover, one study also used urokinase.[7] The average ASPECTS at baseline ranged from 3 to 4, and the core infarct volume ranged from 59.24 mL to 106.01 mL.[7-9] The rate of procedural complications, including arterial dissections, perforations, and arterial access site complications, was 12.2% (n=62/509) among the EVT group from all studies.[7-9]

Risk of bias assessment

All RCTs used adequate randomization generation methods, reported less than 10% missing outcome data, and blinded outcome assessment; however, participants or providers were not blinded given the need for EVT. Most RCTs were rated as low risk of bias but one RCT was rated as high risk of bias due to inadequate randomization methods. Additionally, some cointerventions were introduced that may have affected study outcomes given the inability to blind participants or providers. Details pertaining to the risk of bias assessment are highlighted in Supplementary Figure 1.

Outcomes for EVT versus medical management only

Functional independence (mRS score 0–2 at 90 days)

All studies reported on functional independence, defined as an mRS score of 0 to 2 at 90 days.[7-9] We found low-certainty evidence suggesting that there is possibly a large increase in the proportion of patients achieving functional independence in the EVT group in comparison to those with medical management

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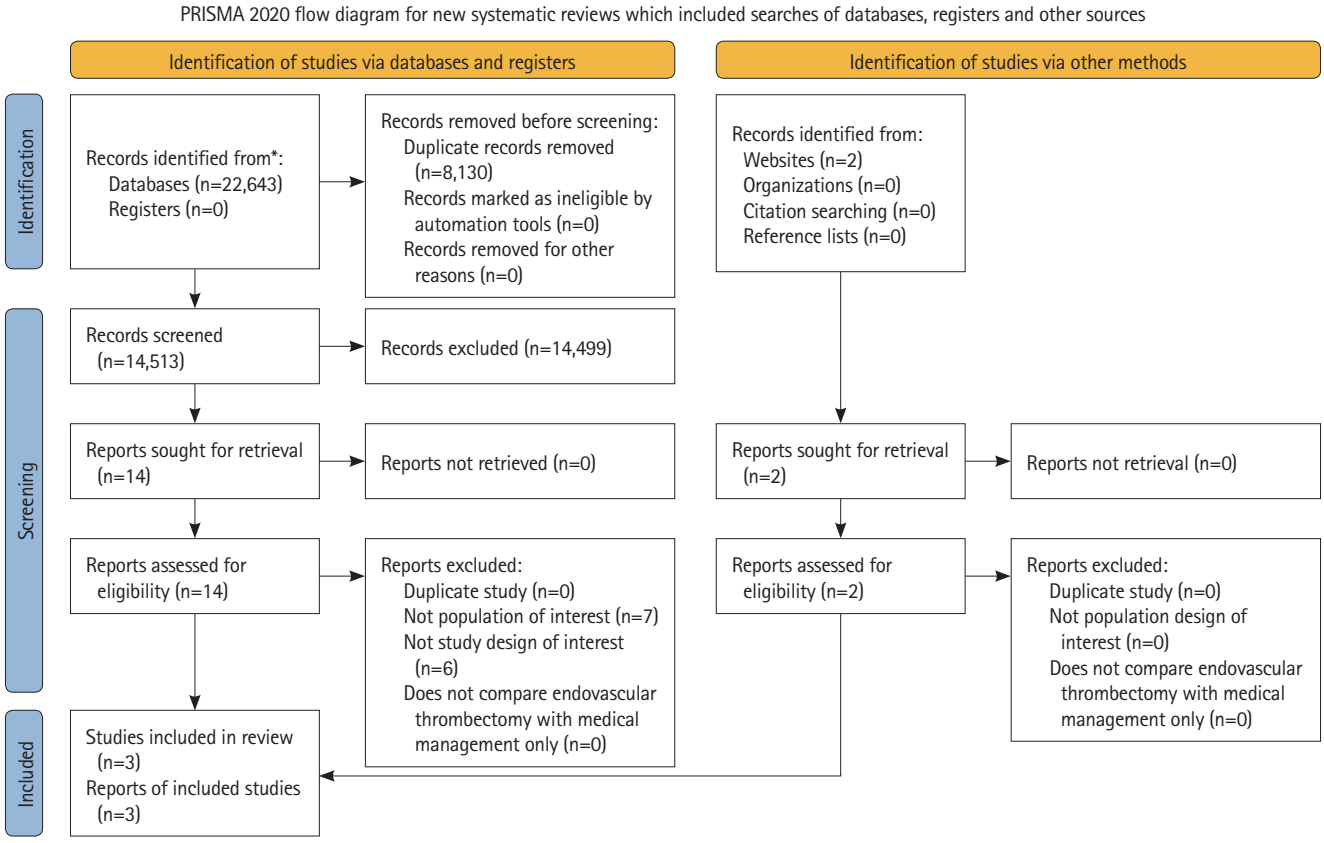

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. *Consider, if feasible to do so, reporting the number of records identified from database or register searched (rather than the total number across all databases/registers). Adapted from Page et al. *J Clin Epidemiol* 2021;134:178-189, under the Creative Commons license (CC-BY).[11] For more information, visit http://www.prisma-statement.org.

only (RR 2.53, 95% CI 1.76 to 3.64; RD 30.3%, 95% CI 15.0% to 52.3%) (Table 2 and Figure 2).

Mortality at 90 days

All studies reported mortality at 90 days.[7-9] We found low-certainty evidence suggesting that there is possibly a small non-significant decrease in mortality at 90 days for patients who underwent EVT compared to those with standard medical management (RR 0.95, 95% CI 0.73 to 1.25; RD -0.7%, 95% CI -3.8% to 3.5%) (Table 2 and Figure 3).

Symptomatic intracranial hemorrhage

All studies reported sICH with differences in the definitions used between studies.[7-9] We found low-certainty evidence suggesting that there is possibly a small non-significant increase in sICH, at least 24 to 48 hours after randomization, in patients who underwent EVT compared to those with medical management only (RR 1.83, 95% CI 0.92 to 3.64; RD 3.1%, 95% CI -0.3% to 9.8%) (Table 2 and Figure 4).

Other secondary outcomes

All studies also reported on mRS of 0 to 3 at 90 days (RR 1.70, 95% CI 1.31 to 2.20) and improvement in the NIHSS score with variability in the definitions (RR 2.44, 95% CI 1.51 to 3.93).[7-9] Only two studies reported on any intracranial hemorrhage (RR 2.41, 95% CI 1.76 to 3.32).[7,9] Further details on these findings are illustrated in Supplementary Figure 2.

Discussion

This systematic review and meta-analysis aimed to evaluate EVT versus medical management alone in AIS patients with large infarct regions. We identified 3 RCTs meeting the inclusion criteria.[7-9] Our analysis produced low-certainty evidence suggesting that EVT possibly increases functional independence, represented by mRS score of 0 to 2, non-significantly decreases mortality, and non-significantly increases the risk of sICH. Imprecision and variability in outcome measurements between studies accounted for most of the quality of evidence assessment.

While there are a few systematic reviews evaluating EVT in AIS patients with large ischemic core volume,[20-22] this meta-anal-

Table 1. Characteristics of included studies

Study ID	Country	Study timeframe	Study design	Sample size (n)	Age, y (mean, SD)	Male (%)	History of stroke (%)	History of atrial fibrillation (%)	History of diabetes (%)	History of hypertension (%)	Initial NIHSS (mean, SD)	Initial ASPECTS (mean, SD)	Infarct core volume, mL (mean, SD)	ICA occlusion (%)	M1 MCA occlusion (%)	M2 MCA occlusion (%)	Tandem occlusion (%)	Intravenous thrombolysis (%)	Type and dose of thrombolytic agent used
Huo 2023[7] [ANGEL-ASPECT]	China	October 2, 2020–May 18, 2022	RCT	455	66.84 (9.72)	61.32	16.04	22.86	18.24	59.78	16 (5)	3 (1)	59.24 (41.76)	36.04	63.08	0.88	16.70	28.35	Alteplase 0.9 mg/kg; urokinase 1.0 to 1.5 million IU
Sarraj 2023[8] [SELECT-2]	International	September 2019–September 2022	RCT	352	66.50 (12.69)	58.81	9.09	24.15	30.68	73.86	19 (6)	4 (1)	84.76 (41.35)	41.48	54.26	4.26	28.41	19.09	Alteplase NOS; tenecteplase NOS
Yoshimura 2022[9] [RESCUE-Japan LIMIT]	Japan	November 2018–September 2021	RCT	203	76.15 (10.09)	55.67	25.12	59.11	21.18	69.46	22 (6)	4 (1)	106.01 (57.50)	47.29	70.94	1.48	19.70	27.59	Alteplase 0.6 mg/kg

SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; MCA, middle cerebral artery; RCT, randomized controlled trial; IU, international unit; NOS, not otherwise specified; ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial.

ysis is the first to incorporate evidence from the most recently published RCTs, namely the ANGEL-ASPECT (Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core), SELECT-2 (A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke), and RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial) trials.[7-9] Moreover, we aim to make this study a living systematic review and meta-analysis to include future RCTs comparing outcomes in AIS patients with large infarct regions who underwent EVT versus medical management only. Our systematic review adhered to full living systematic review methodology, used rigorous methods in screening regardless of language, assessed for certainty of evidence using the GRADE approach, and evaluated the risk of bias using the RoB 2 tool. We engaged research methodologists and content experts to facilitate absolute risk quantification by imputing RDs for a more comprehensive interpretation of the results.

Although the results of this meta-analysis showed that EVT may be considered as an option in AIS patients with large ischemic core regions compared to standard medical management, there are certain distinctions that need to be made. RCTs were included regardless of the diagnostic modality used to identify large strokes. This distinction is important to make because bias can be introduced if studies using different diagnostic modalities other than baseline ASPECTS as an inclusion criterion are not included. While the baseline ASPECTS was considered when enrolling patients in the ANGEL-ASPECT, RESCUE-Japan LIMIT, and SELECT-2, the SELECT-2 trial used computed tomography perfusion or magnetic resonance imaging perfusion with any core volume greater than 50 mL in addition to ASPECTS to define large strokes.[7-9] Compared to other systematic reviews and meta-analyses, this study is focused more on patient-important outcomes rather than surrogate outcomes, such as any intracranial hemorrhage and successful reperfusion on final angiogram. There is a gap between surrogate endpoints and interpretation of these surrogate endpoints in clinical practice, and we focused on hard endpoints rather than surrogate endpoints to inform patient-centered care.[19,23] While we reported surrogate endpoints, such as any intracranial hemorrhage, we did not incorporate this data into our evidence assessment. Additionally, the included trials in this meta-analysis used different definitions of outcomes. The ANGEL-ASPECT trial defined sICH according to the Heidelberg Bleeding Classification,[7] SELECT-2 used the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria,[8] and the RESCUE-Japan LIMIT trial defined sICH as parenchymal hematoma type 2 encompassing at least 30% of the infarcted area in conjunction with worsening of the NIHSS score by at

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Table 2. GRADE evidence profile for all RCTs comparing outcomes for acute ischemic stroke patients who underwent EVT versus medical management only

Outcomes of all RCTs[7-9]	Certainty assessment			No. of patients		Effect			Certainty	Importance
	Inconsistency	Indirectness	Imprecision	Endovascular therapy	Medical management only	RR (95% CI)	Baseline risk for control group (%)*	RD (%) (95% CI)		
Functional independence at 90 days	Not serious	Not serious	Very serious†	119/507 (23.5%)	46/498 (9.2%)	2.53 (1.76 to 3.64)	19.8	30.3 (15.0 to 52.3)	⨁⨁◯◯ Low	CRITICAL
Mortality at 90 days	Not serious	Not serious	Very serious†	136/507 (26.8%)	140/498 (28.1%)	0.95 (0.73 to 1.25)	14.0	-0.7 (-3.8 to 3.5)	⨁⨁◯◯ Low	CRITICAL
Symptomatic intracranial hemorrhage	Not serious	Not serious	Very serious†	24/508 (4.7%)	13/501 (2.6%)	1.83 (0.92 to 3.64)	3.7	3.1 (-0.3 to 9.8)	⨁⨁◯◯ Low	IMPORTANT

GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; RCTs, randomized controlled trials; EVT, endovascular thrombectomy; RR, risk ratio; CI, confidence interval; RD, risk difference.
*The baseline risk for each outcome was retrieved from a study comparing EVT versus medical management alone in patients presenting with a large vessel occlusion in the anterior circulation; †Some studies included a total sample size of less than 300.

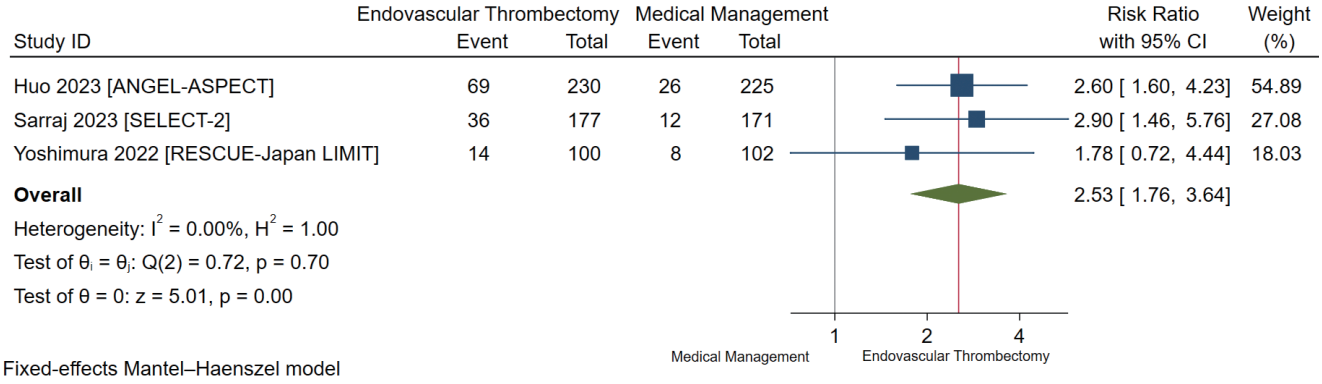

Figure 2. Forest plot for endovascular thrombectomy versus medical management only for functional independence defined as modified Rankin Scale score of 0 to 2 at 90 days. ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial; CI, confidence interval.

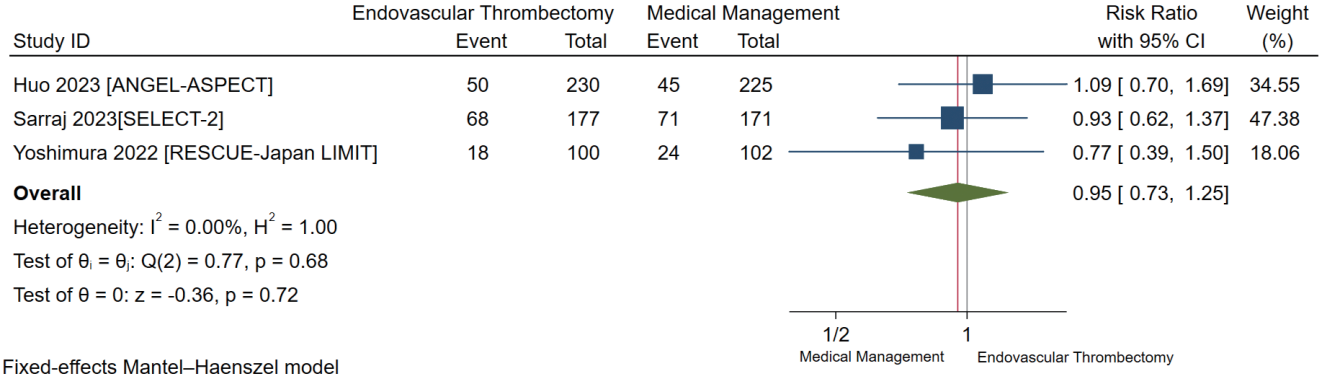

Figure 3. Forest plot for endovascular thrombectomy versus medical management only for mortality at 90 days. ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial; CI, confidence interval.

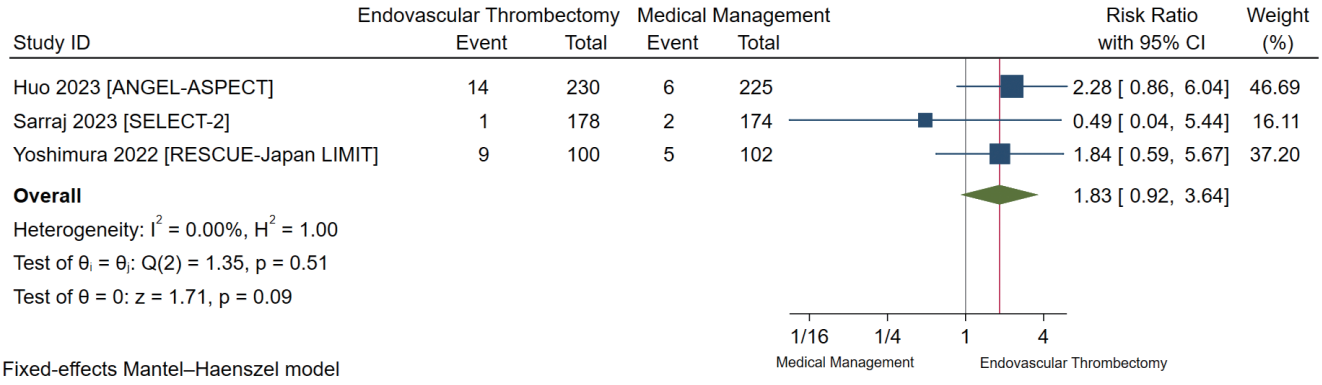

Figure 4. Forest plot for endovascular thrombectomy versus medical management only for symptomatic intracranial hemorrhage. ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial; CI, confidence interval.

least 4 points within 48 hours.[9] Taking this variability of definitions into consideration, our pooled effect estimates did not show any statistical heterogeneity (I^2=0%), thus making our conclusion such that EVT possibly increases the risk of sICH compared to medical management only. Finally, unlike prior systematic reviews, this is the first living systematic review on the topic given the anticipation for future trials addressing our question even further.

Factors that were not accounted for in this meta-analysis were the inability to perform a meta-regression analysis due to the number of studies and inadequate power, the inability to perform subgroup analyses based on certain characteristics, such as simultaneous presence of ipsilateral extracranial (or tandem) occlusions or type of intravenous thrombolytic agent used, and the inability to account for ordinal mRS shifts in our meta-analysis, which may serve as better measures for long-term endpoints compared to dichotomous endpoints.[24]

Although our meta-analysis only included data from RCTs, it serves as a snapshot of the highest quality evidence available comparing EVT to standard medical management in AIS patients with large ischemic regions. It is important to understand that while these RCTs had differences in study design, patient inclusion criteria, imaging selection criteria, and thrombolytic agent type and dosing, outcomes were comparably similar. Additionally, two RCTs considered ordinal shift in mRS at 90 days as their primary outcome,[7,8] and one RCT considered an mRS score of 0 to 3 at 90 days after stroke onset as the primary outcome.[9] Although EVT may be considered in death prevention, it may be associated with severe post-procedural functional deficits when factoring the benefits of EVT on the basis of an ordinal mRS shift.[25] Patients who underwent EVT had a shift towards improved outcomes in other categories based on the results of these trials, but mortality was still high ranging from 7.8% to 38.4% among the EVT group.[7-9] Our results also demonstrated low-certainty evidence suggesting a possible small increase in sICH among patients who underwent EVT compared to medical management only. While the SELECT-2 trial had the lowest risk of sICH compared to the other two included trials, patients who underwent EVT had higher rates of early neurologic worsening on exam, which could be speculated as post-procedural reperfusion-related edema.[7-9] This anticipated risk of sICH should be discussed with patients and caregivers and weighed against the possible increase in functional outcomes. It is also difficult to interpret the cost utility behind the use of EVT compared to standard medical management in this patient population, but one could extrapolate the greater costs for the required care of these patients. Of noteworthy importance, ANGEL-ASPECT did not enroll patients with ischemic core volumes larger than 70 mL to 100 mL with an ASPECTS greater than 5, and RESCUE-Japan LIMIT and SELECT-2 excluded AIS patients with ASPECTS less than 3; as such, outcomes and costs may vary if these subgroups are explored. Evidence from future trials, such as LASTE (Large Stroke Therapy Evaluation), TENSION (Efficacy and Safety of Thrombectomy in Stroke with Extended Lesion and Extended Time Window), and TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke),[26] might help address the unanswered questions. Therefore, clinicians and guideline developers should cautiously interpret the results of this systematic review and meta-analysis when considering EVT for large strokes.

Conclusions

In conclusion, our living systematic review and meta-analysis examined the benefits and safety of EVT compared to medical management in AIS-LVO patients with large infarct regions. We found low-certainty evidence that EVT possibly increases func-

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tional independence, non-significantly decreases mortality, and non-significantly increases the risk of sICH. Evidence from anticipated future trials will further determine whether these outcomes remain valid.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.00752.

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None

Conflicts of interest

The authors completed the ICMJE Disclosure Forms and declare no competing interests.

Author contribution

Conceptualization: RZM, ME, FA, TK. Study design: RZM, ME, HSG. Methodology: RZM, ME, HSG. Data collection: RZM, ME, HSG, MA, AE, SK, HD. Investigation: all authors. Statistical analysis: RZM, HSG. Writing—original draft: RZM, ME, HSG. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist

Section and topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3-4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3-4
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Figure 1

Supplementary Table 1. Continued

Section and topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5, Supplementary Figure 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	4, 7
	23b	Discuss any limitations of the evidence included in the review.	7
	23c	Discuss any limitations of the review processes used.	7
	23d	Discuss implications of the results for practice, policy, and future research.	4, 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	8
Competing interests	26	Declare any competing interests of review authors.	8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	8

Supplementary Table 2. Search algorithms for MEDLINE (through Ovid), Embase, and Cochrane Library

	Search strategy
Search algorithm for MEDLINE (through Ovid)[a]	
1	exp Thrombectomy/ or (((Thrombophlebit?s or Thrombos?s) adj4 surger*) or Thrombectom* or (Surg* and remov* and EMBOLECTOM*)).mp. (19914)
2	Mechanical Thrombolysis/ or ((Mechani* adj3 (disrupt* or Thromb*)) or (procedur* and disintegrate* and THROMB*)).mp. (16235)
3	EMBOLECTOMY/ or (EMBOLECTOM* or (emboliism adj4 surger*)).mp. (4246)
4	Endovascular Procedures/ or ((Endovascular or intravenous) and (therap* or reperfusion or treat* or procedur* or techni* or surg*)).mp. (362172)
5	or/1-4 (388348)
6	Stroke/ or Thrombotic Stroke/ or Ischemic Stroke/ or Embolic Stroke/ or Stroke, Lacunar/ (132587)
7	(((infarct* or infract* or syndrome*) adj2 (thrombo* or Lacunar or Embolic or Ischemic)) or Stroke* or ((Cerebrovascular or vascular) adj2 Accident*) or CVA* or Apoplex*).mp. (386512)
8	Brain Ischemia/ or Brain Infarction/ (65143)
9	((Cerebr* or Encephalopath* or Brain or Subcortical or "Anterior Choroidal Artery" or "Posterior Choroidal Artery") adj4 (ischem* or Infarct* or Infract*)).mp. (141949)
10	6 or 7 or 8 or 9 (458790)
11	5 and 10 (30573)

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Supplementary Table 2. Continued

	Search strategy
12	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1366192)
13	11 and 12 (4955)
Search algorithm for Embase	
#1	'mechanical thrombectomy'/de OR 'thrombectomy'/de (41329)
#2	(((thrombophlebit$s OR thrombos$s) NEAR/4 surger*):ti,ab,kw) OR thrombectom*:ti,ab,kw OR (surg*:ti,ab,kw AND remov*:ti,ab,kw AND embolectom*:ti,ab,kw) (29726)
#3	((mechani* NEAR/3 (disrupt* OR thromb*)):ti,ab,kw) OR (procedur*:ti,ab,kw AND disintegrate*:ti,ab,kw AND thromb*:ti,ab,kw) (24544)
#4	'embolectomy'/de OR embolectom*:ti,ab,kw OR ((emboliism NEAR/4 surger*):ti,ab,kw) (7578)
#5	'endovascular surgery'/de OR ((endovascular:ti,ab,kw OR intravenous:ti,ab,kw) AND (therap*:ti,ab,kw OR reperfusion:ti,ab,kw OR treat*:ti,ab,kw OR procedur*:ti,ab,kw OR techni*:ti,ab,kw OR surg*:ti,ab,kw)) (391352)
#6	#1 OR #2 OR #3 OR #4 OR #5 (440991)
#7	'cerebrovascular accident'/de OR 'ischemic stroke'/de OR 'embolic stroke of undetermined source'/de OR 'embolic stroke of unknown source'/de OR 'cardioembolic stroke'/de OR 'lacunar stroke'/de (403332)
#8	'brain ischemia'/de OR 'brain infarction'/de (205716)
#9	((cerebr* OR encephalopath* OR brain OR subcortical OR 'anterior choroidal artery' OR 'posterior choroidal artery') NEAR/4 (ischem* OR infarct* OR infract*)):ti,ab,kw (130233)
#10	#7 OR #8 OR #9 (743473)
#11	#6 AND #10 (54294)
#12	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo* (2815499)
#13	#11 AND #12 (12110)
Search algorithm for Cochrane Library	
#1	MeSH descriptor: [Thrombectomy] explode all trees (550)
#2	((((Thrombophlebit?s or Thrombos?s) NEAR/3 surger*) or Thrombectom* or (Surg* and remov* and EMBOLECTOM*))):ti,ab,kw (2707)
#3	MeSH descriptor: [Mechanical Thrombolysis] this term only (53)
#4	(((Mechani* NEAR/2 (disrupt* or Thromb*)) or (procedur* and disintegrate* and THROMB*))):ti,ab,kw (935)
#5	MeSH descriptor: [Embolectomy] this term only (18)
#6	((EMBOLECTOM* or (emboliism NEAR/3 surger*))):ti,ab,kw (141)
#7	MeSH descriptor: [Endovascular Procedures] this term only (808)
#8	(((Endovascular or intravenous) and (therap* or reperfusion or treat* or procedur* or techni* or surg*))):ti,ab,kw (86495)
#9	{OR #1-#8} (88318)
#10	MeSH descriptor: [Stroke] this term only (12830)
#11	MeSH descriptor: [Thrombotic Stroke] this term only (3)
#12	MeSH descriptor: [Ischemic Stroke] this term only (624)
#13	MeSH descriptor: [Embolic Stroke] this term only (18)
#14	MeSH descriptor: [Stroke, Lacunar] this term only (54)
#15	(((infarct* or infract* or syndrome*) NEAR/1 (thrombo* or Lacunar or Embolic or Ischemic)) or Stroke* or ((Cerebrovascular or vascular) NEAR/1 Accident*) or CVA* or Apoplex*):ti,ab,kw (71262)
#16	MeSH descriptor: [Brain Ischemia] this term only (2394)
#17	MeSH descriptor: [Brain Infarction] this term only (129)
#18	(((Cerebr* or Encephalopath* or Brain or Subcortical or "Anterior Choroidal Artery" or "Posterior Choroidal Artery") NEAR/3 (ischem* or Infarct* or Infract*))):ti,ab,kw (13902)
#19	{OR #10-#18} (76034)
#20	#9 AND #19 (6529)

[a]Database: Ovid MEDLINE® Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 10, 2021>.

Supplementary Figure 1. Risk of bias assessment. (A) Revised Cochrane risk-of-bias tool (RoB2). (B) Risk of bias summary. ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial.

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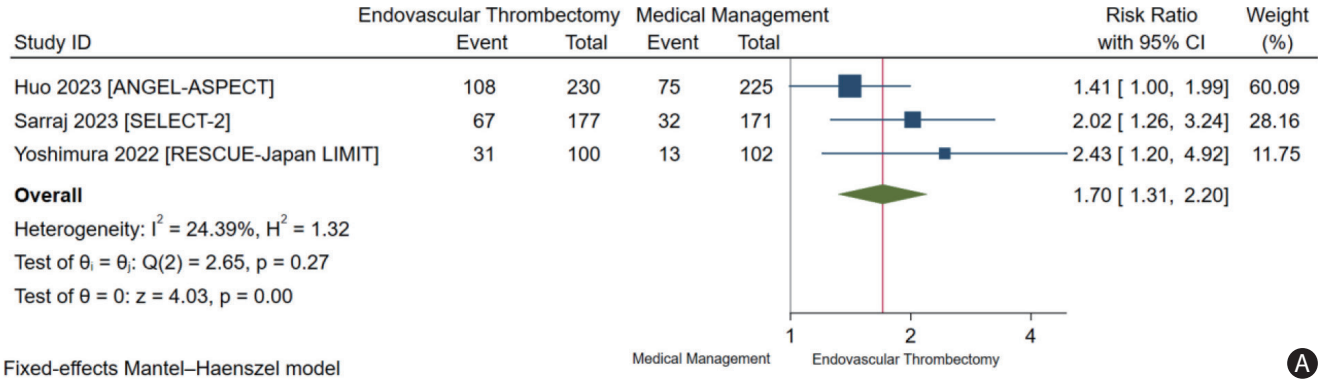

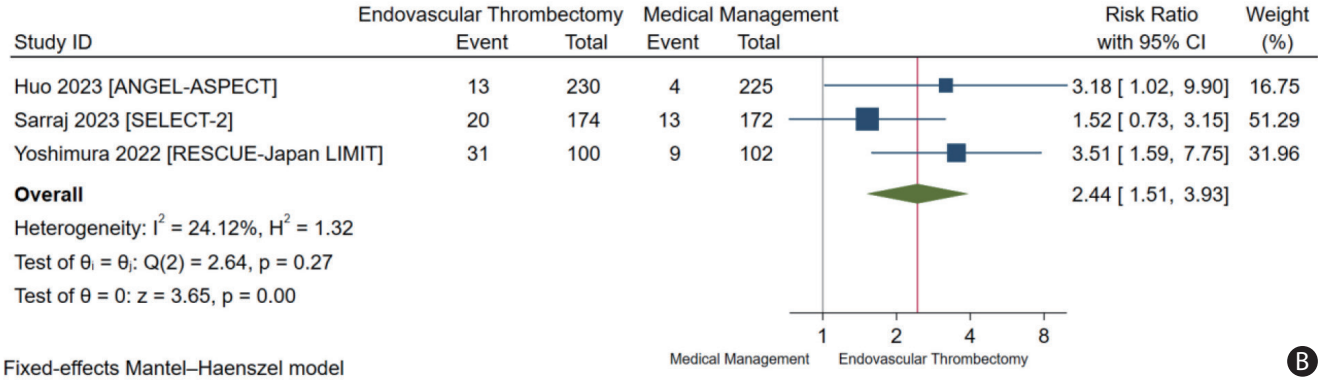

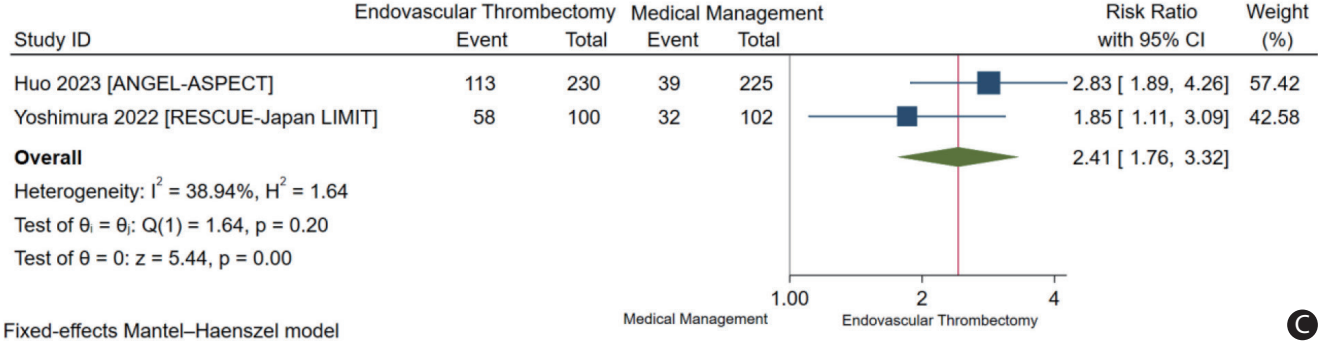

Supplementary Figure 2. Other secondary outcomes. (A) Modified Rankin Scale score 0 to 3 at 90 days. (B) Improvement in National Institutes of Health Stroke Scale score. (C) Any intracranial hemorrhage. ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; SELECT-2, A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial; CI, confidence interval.