# SYSTEMATIC REVIEW UPDATE

# Endovascular thrombectomy after anterior circulation large vessel ischemic stroke: an updated meta-analysis

Seraj Makkawi<sup>1,2,3\*</sup>, Jawad I. Bukhari<sup>1,2</sup>, Hassan K. Salamatullah<sup>1,2</sup>, Osama A. Alkulli<sup>1,2</sup>, Abdulrahman E. Alghamdi<sup>1,2</sup>, Asim Bogari<sup>1,2</sup>, Naif M. Aloufi<sup>1,2</sup>, Mohammed Albadri<sup>1,2</sup>, Fay N. Alnafisi<sup>1,2</sup> and Saeed Alghamdi<sup>4</sup>

# Abstract

**Background** Endovascular thrombectomy (EVT) has emerged as the established standard of care for the treatment of anterior circulation large-vessel occlusion (LVO). However, its benefits remain unclear in specific patient populations. Herein, we present an updated systematic review and meta-analysis aimed at thoroughly assessing the effectiveness and safety of combining EVT with medical treatment (MT) compared with MT alone.

**Methods** This systematic review was performed in accordance with the PRISMA guideline. The MEDLINE, Embase, and Cochrane databases were systematically searched to identify relevant articles published until December 30, 2023. The inclusion criteria restricted articles to randomized clinical trials (RCTs). We pooled odds ratios (OR) and their respective 95% confidence intervals (CIs).

**Results** Fifteen RCTs involving 3897 patients were included in the study. EVT plus MT was associated with a significant reduction in disability at 90 days (OR = 1.91, [1.61–2.26]), improved functional independence (modified Rankin Scale [mRS] 0–2) (OR = 2.19 [1.81–2.64]), excellent functional outcomes (mRS 0–1) (OR = 2.37, [1.45–3.87]), improved independent ambulation (mRS 0–3) (OR = 2.17, [1.75–2.69]), and higher rates of partial/complete recanalization (OR = 2.18, [1.66–2.87] compared with EVT. Efficacy outcomes for both large and small infarct cores were statistically favorable following EVT. Safety outcomes showed comparable rates, except for intracerebral and subarachnoid hemorrhage, which favored MT alone.

**Conclusion** This meta-analysis supports the use of EVT plus MT as the standard of care for acute ischemic stroke patients with LVO of any infarct core size, as it offers substantial improvements in functional outcomes and recanalization. Safety considerations, particularly the risk of hemorrhage, warrant careful patient selection. These findings provide valuable insights for optimizing stroke management protocols and enhancing patient outcomes.

Keywords Large vessel ischemic stroke, Endovascular thrombectomy, Meta-analysis, Anterior circulation

\*Correspondence: Seraj Makkawi serajmakkawi@gmail.com Full list of author information is available at the end of the article







© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

# Introduction

Acute ischemic stroke (AIS) is a severe neurological emergency with significant global health implications, primarily due to associated large-vessel occlusion (LVO) [1]. While intravenous thrombolysis (tPA) has been considered the standard treatment for AIS, its efficacy in LVO cases is limited, and it has a narrow treatment window [2, 3]. As such, there is an urgent need to explore more effective therapies, including the best medical treatments for this high-risk patient group. Endovascular thrombectomy (EVT) has recently emerged as a groundbreaking intervention for AIS with LVO in the context of optimal medical treatment [3]. This technique involves the mechanical removal of thrombi from blocked brain vessels, the restoration of blood flow, and the preservation of ischemic brain tissue. Advancements in stent retrieval and imaging technologies have revolutionized stroke management [4]. Numerous randomized clinical trials (RCTs) have previously investigated the efficacy and safety of EVT in patients with AIS LVO [5-15], reporting promising functional outcomes and overall improvements in patient prognosis with a combination of the best medical treatment (MT) and EVT. However, despite the growing evidence supporting EVT, there remains a critical need for a comprehensive analysis of the collective data from these trials to draw robust conclusions regarding its efficacy and safety.

A systematic review and meta-analysis on this topic would provide a more comprehensive understanding of the impact of treatment on functional outcomes, safety profiles, and other relevant measures associated with AIS due to LVO in the context of the best medical treatment. The findings of the present meta-analysis could thus potentially affect stroke care practices, leading to improved patient outcomes and reduced long-term disability in this high-risk population. By offering a comprehensive evaluation of the available evidence, this meta-analysis seeks to inform stroke care guidelines and ultimately benefit numerous patients with AIS and their families. The results of this study will help to consolidate evidence supporting the efficacy and safety of EVT, strengthening its establishment as a standard of care for AIS with LVO, thus transforming stroke management and improving patient outcomes.

# Methods

This study was registered in the PROSPERO (CRD42023423020) database prior to the preliminary search and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Furthermore, this study did not require ethical

approval as the data have been published previously. All data are available in this article.

# **Eligibility criteria**

This systematic review and meta-analysis included only RCTs that used vessel imaging to include patients with vessel occlusion in one of the following locations: the internal carotid artery (ICA), middle cerebral artery segment 1 (M1), or middle cerebral artery segment 2 (M2). In all the included studies, patients were randomized to receive either EVT plus MT or MT alone.

# Search strategy

We systematically searched the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CEN-TRAL) databases from database initiation until December 30, 2023, without any restrictions on date or language. All databases were searched with keywords including "ischemic stroke" OR "stroke" OR "acute ischemic stroke" AND "Endovascular treatment" OR "mechanical thrombectomy" OR "thrombectomy" AND "large vessel occlusion" OR "Large vessel ischemia" OR "large artery occlusion" AND "thrombolytics" OR "thrombolysis" AND "randomized clinical trials." Manual searches of the reference lists from recent systematic reviews and published studies were also performed to identify any eligible studies missed during screening.

# Study selection and data extraction

After excluding duplicates, two authors independently screened the articles by title, abstract, and full-text evaluation to identify articles eligible for inclusion based on the criteria. Disagreements at both stages were clarified by a consensus or by a third author. Data were extracted using a predetermined Excel spreadsheet. Data were extracted according to the following protocol variables: study characteristics, design, number of subjects, inclusion and exclusion criteria, demographic data of participants, baseline characteristics, imaging and treatment details of interest, efficacy, and safety outcomes.

# Study outcomes

The efficacy outcomes of this meta-analysis included the overall ordinal shift across the range of degree of disability on the modified Rankin Scale (mRS) at 90 days, which categorizes patient disability on scores ranging from 0 (no symptoms) to 6 (death). The mRS is a widely used measure of functional outcome following stroke, with established reliability and validity [16]. We further assessed functional independence (defined as mRS score of 0-2 at 90 days), excellent functional outcome (defined as mRS score of 0-3 at 90 days), independent ent ambulation (defined as mRS score of 0-3 at 90 days),

early neurological improvement (ENI) as defined for each study (Supplementary Table 1), Barthel Index score of 95–100 at 90 days, and partial/complete recanalization as defined for each study (Supplementary Table 1). The safety outcomes included any intracerebral hemorrhage (ICH), symptomatic intracranial hemorrhage (sICH) (Supplementary Table 1), mortality at 90 days, early neurological worsening (ENW) as defined in each study (Supplementary Table 1), parenchymal hematoma type 1, parenchymal hematoma type 2, and subarachnoid hemorrhage.

# Risk of bias and quality assessment

Two reviewers used the Revised Cochrane Risk-of-Bias 2 tool (RoB2) to independently evaluate the risk of bias in all eligible RCTs. Any disagreements were resolved by discussion with a third author.

# Statistical analysis

Data from the included trials were analyzed using Rev-Man (Review Manager) version 5.4.1 (Cochrane Collaboration). The effect sizes for the intended outcomes were combined using the inverse variance method for generic variance or dichotomous data, as appropriate, with a random effects model to calculate the overall effect size. The threshold for statistical significance was set at a 95% confidence level or P < 0.05. Statistical heterogeneity was assessed using the  $I^2$  and *P*-values of the chi-squared test. When  $I^2$  was > 50%, sensitivity analysis was conducted by excluding each study at a time, and the highest change was reported. Subgroup analysis was further performed based on the infarct core size to identify the effect of the intervention on functional independence, partial/complete recanalization, sICH, rates of any ICH, and mortality. Furthermore, a subgroup analysis was performed based on age to observe the change in mRS scores at 90 days. Publication bias was further assessed based on a visual inspection of the symmetrical distribution of the included studies. For the asymmetrical distributions, Egger's regression and Begg's rank correlation tests were conducted to confirm the results.

# Results

# Search result and study selection

The initial database search using the aforementioned keywords yielded 3695 articles, which decreased to 2915 articles after removing duplicates. After completing the title and abstract screening, 29 studies were included in the full-text screening. Eight articles were included in this study, with an additional seven identified by screening the citations of the included articles. Finally, 15 RCTs were included in the meta-analysis (Fig. 1).



Fig. 1 PRISMA flowchart

# Study baseline characteristics

Fifteen RCTs with 3897 patients met the inclusion criteria and were included in the meta-analysis. Of the patient cohort, 1939 were allocated to the intervention group (EVT + MT) and 1958 to the control group (MT alone). Thirteen RCTs were multicenter studies, whereas that by Khoury was a single-center study [4]. Table 1, Supplementary Table 2, and Supplementary Table 3 show the demographic characteristics, reported comorbidities, definition of the infarct core for each study, and baseline characteristics for all 16 included RCTs. A summary of the results of risk-of-bias assessment is shown in Supplementary Fig. 1.

# mRS ordinal shift distribution at 90 days

Thirteen RCTs reported an ordinal shift analysis of the mRS distribution. After pooling the results of the ordinal shift distribution, EVT plus MT was associated with a significant reduction in disability at 90 days over MT alone (OR=1.91, 95% *CI* [1.61–2.26]), P<0.00001,  $I^2$ =54%) (Fig. 2A). In sensitivity analysis, removing the study of Goyal et al. [11] resulted in a significant decrease in heterogeneity (OR=1.79, 95% *CI* [1.53–2.10]), P<0.00001,  $I^2$ =42%) (Supplementary Fig. 2). A sub-group analysis of four RCTs based on age, both with groups patients less than 70 years old and 70 years or older, demonstrated significant difference favoring intervention with homogenous effects (OR=1.72, 95% *CI* [1.40–2.11], P<0.00001,  $I^2$ =0%) and (OR=1.40, 95% *CI* [1.11–31.77], P=0.004,  $I^2$ =0%), respectively (Supplementary Fig. 3).

# Excellent functional outcome (mRS 0-1) at 90 days

Four RCTs reported excellent functional outcomes between the two groups. EVT plus MT was found to be significantly associated with excellent functional outcome with homogenous effects (OR=2.37, 95% *CI* [1.45–3.87], P=0.0006,  $l^2$ =0%) (Fig. 2B).

### Functional independence (mRS 0-2) at 90 days

All RCTs investigated the differences between EVT plus MT and EVT alone. The pooled analysis showed that EVT plus MT was significantly associated with functional independence (OR=2.19, 95% *CI* [1.81–2.64], P < 0.00001,  $I^2 = 46\%$ ) (Fig. 2C). Visual inspection revealed that the studies were skewed to the right, resulting in an asymmetrical distribution in the funnel plot (Supplementary Fig. 4). Egger's regression test for funnel plot asymmetry yielded a *t*-statistic of 2.3625, with a *p*-value of 0.0359, presenting evidence of asymmetry. Begg's rank correlation test revealed a *z*-statistic of 1.92 with a *P*-value of 0.0554, indicating borderline evidence of funnel plot asymmetry (Supplementary Fig. 5). Infarct

core-based analysis was further performed. Patients with both large and small infarct cores treated with EVT plus MT showed significant improvement in functional independence at 90 days (OR=2.50, 95% *CI* [1.76–3.54], P<0.00001,  $I^2=26\%$ ) and (OR=2.27, 95% *CI* [1.67–3.08], P<0.00001,  $I^2=57\%$ ), respectively (Fig. 3).

# Independent ambulation (mRS 0-3) at 90 days

Five RCTs reported differences in independent ambulation at 90 days between the two groups. EVT plus MT was significantly associated with independent ambulation with a homogenous effect (OR=2.17, 95% *CI* [1.75– 2.69], P<0.00001,  $I^2$ =6%) (Fig. 2D).

# Early neurological improvement (ENI)

A pooled analysis of nine RCTs comparing the two groups showed that EVT plus MT was significantly associated with ENI compared with MT alone (OR=3.28, 95% *CI* [2.47–4.34], P<0.00001,  $I^2$ =39%) (Fig. 2E).

A pooled analysis of three RCTs comparing the two groups showed that EVT plus MT was significantly associated with a Barthel Index score of 95–100 at 90 days compared with MT alone, with a homogeneous effect (OR=2.53, 95% *CI* [1.83–3.52], P<0.00001,  $I^2$ =29%) (Fig. 2F).

# Barthel Index score of 95-100 at 90 days

A pooled analysis of three RCTs comparing the two groups showed that EVT plus MT was significantly associated with a Barthel Index score of 95–100 at 90 days compared with MT alone, with a homogeneous effect (OR=2.53, 95% *CI* [1.83–3.52], P<0.00001,  $I^2$ =29%) (Fig. 2F).

# Partial/complete recanalization

Six RCTs encompassing 1401 patients reported differences in partial and complete recanalization. EVT plus MT demonstrated statistically significant higher rates in achieving partial/complete recanalization of occluded vessels (OR=2.18, 95% CI [1.66-2.87], P<0.00001,  $I^2 = 84\%$ ) (Supplementary Fig. 6). In the sensitivity analysis, removing Brekhemer et al. [13] resulted in the most significant change in heterogeneity, which was deemed as moderate heterogeneity (OR=2.37, 95% CI [1.92-2.93], P < 0.00001,  $I^2 = 54\%$ ) (Supplementary Fig. 7). Infarct core-based analysis was further performed. Large infarct core and small infarct core patients who treated with EVT plus MT showed higher rates of partial/complete recanalization (OR=2.47, 95% [1.99-3.06], P<0.00001) and  $(OR = 2.37, 95\% [1.76 - 3.21], P < 0.00001, I^2 = 64\%)$ , respectively (Fig. 4).

lable 1 base	eline patient cr	naracteristics of	included studie	S							
Studies (author, publication year)	Country	Study design	No. of patients	Gender Male [ <i>n</i> (%)]	Female [ <i>n</i> (%)]	Median age (IQR), mean±SD	Baseline NIHSS score mean (SD)	ASPECTS on baseline CT mean (SD)	Internal carotid artery occlusion [ <i>n</i> (%)]	M1 segment middle cerebral artery occlusion [ <i>n</i> (%)]	M2 segment middle cerebral artery occlusion [ <i>n</i> (%)]
Huo (2023) [15]	China	RCT	MM: 225 EVT + MM: 230	MM: 144 (64.0) EVT + MM: 135 (58.7)	MM: 81 (36) EVT + MM: 95 (41.3)	MM: 67 (59–73) EVT+MM: 68 (61–73)	MM: 15 (12–19) EVT+MM: 16 (13–20)	MM: 3 (3-4) EVT+MM: 3 (3-4)	MM: 81 (36.0) EVT + MM: 83 (36.1)	MM: 142 (63.1) EVT + MM: 145 (63.0)	MM: 2 (0.9) EVT + MM: 2 (0.9)
Sarraj (2023) [5]	USA	RCT	MM: 174 EVT + MM: 178	MM: 98 (57.0) EVT+MM: 109 (60.6)	MM: 74 (42.5) EVT + MM: 71 (39.9)	MM: 67 (58–75) EVT+MM: 66 (58–75)	MM: 19 (15–22) EVT + MM: 19 (15–23)	MM: 4 (4-5) EVT+MM: 4 (3-5)	MM: 66 (38.4) EVT + MM: 80 (44.4)	MM: 98 (57.0) EVT + MM: 93 (51.7)	MM: 8 (4.7) EVT + MM: 7 (3.9)
Bendszus (2023) [17]	Worldwide	RCT	MM: 128 EVT+MM: 125	MM: 51 (48.0) EVT + MM: 59 (55)	MM: 67 (52) EVT + MM: 56 (45)	MM: 74 (64–80) EVT+MM: 73 (65–81)	MM: 18 (15–22) EVT+MM: 19 (16–22)	NR	MM: 37 (29) EVT + MM: 41 (33)	MM: 88 (69) EVT + MM: 83 (66)	MM: 7 (5) EVT + MM: 0 (0)
Albers (2018) [18]	USA	RCT	MM: 90 EVT + MM: 92	NR	MM: 46 (51) EVT + MM: 46 (50)	MM: 71 (95–80) EVT + MM: 70 (59–79)	MM: 16 (12–21) EVT + MM: 16 (10–20)	MM:8 (7-9) EVT+MM:8 (7-9)	MM: 36 (40) EVT + MM: 32 (35)	MM: 54 (60) EVT + MM: 60 (6	5) <sup>a</sup>
Nogueria (2018) [19]	Worldwide	RCT	MM:99 EVT+MM: 107	MM: 51 (52) EVT + MM: 42 (39)	NR	MM: 70.7 (13.2) EVT + MM: 69.4 (14.1)	MM: 17 (13–21) EVT + MM: 17 (14–21)	NR	MM: 19 (19) EVT+MM: 22 (21)	MM: 77 (78) EVT + MM: 83 (78)	MM: 2 (2) EVT+MM: 3 (3)
Yoshimura (2022) [14]	Japan	RCT	MM: 102 EVT + MM: 101	MM: 58 (56.9) EVT + MM: 55 (54.5)	MM: 44 (43.1) EVT + MM: 46 (45.5)	MM: 75.7 ± 10.2 EVT + MM: 76.6 ± 10.0	MM: 22 (17–26) EVT + MM: 22 (18–26)	MM: 4 (3-4) EVT + MM: 3 (3-4)	MM: 49 (48.0) EVT + MM: 47 (46.5)	MM: 70 (68.6) EVT + MM: 74 (73.3)	MM: 3 (2.9) EVT+MM: 0
Khoury (2017) [7]	Canada	RCT	MM: 37 EVT + MM: 40	MM: 20 (54.1) EVT + MM: 18 (45)	MM: 17 (45.9) EVT + MM: 22 (55.0)	MM: 71 (59–79) EVT + MM: 74 (62.7–80)	MM: 20 (12.00–23.00) EVT + MM: 18 (13.00–21.75)	MM: 9 (8-9) EVT+MM: 8 (7-9)	MM: 2 (5.4) EVT + MM: 6 (15.0)	MM: 24 (64.9) EVT + MM: 17 (42.5)	MM: 6 (16.2) EVT + MM: 12 (30.0)
Mocco (2016) [9]	USA	RCT	MM: 62 EVT + MM: 43	MM: 23 (43) EVT + MM: 34 (62)	MM: 30/53 (57) EVT + MM: 21/55 (38)	MM: 70 (10) EVT + MM: 67 (11)	MM: 18 [14.22] EVT+MM: 17 [13.22]	MM: 8.0 (7–9) EVT + MM: 7.5 (6–9)	MM: 23% (12/53) EVT + MM: 33% (18/55)	MM: 68% (36/53) EVT + MM: 56% (31/55)	MM: 9.4% (5/53) EVT + MM: 11% (6/55)
Muir (2017) [6]	UK	RCT	MM: 32 EVT + MM: 33	MM: 16 (50) EVT+MM: 13 (39)	MM: 16 (50) EVT + MM: 20 (61)	MM: 64±16 EVT+MM: 67±17	MM: 14 (6–29) EVT + MM: 18 (6–24)	MM: 9 (2-10) EVT+MM: 9 (4-10)	MM: 6 (19) EVT + MM: 4 (14)	MM: 21 (65) EVT + MM: 22 (76)	MM: 5 (16) EVT + MM: 3 (10)

Studies	Country	Study design	No. of	Gender		Median	Baseline	ASPECTS on	Internal	M1 segment	M2 segment
(author, publication year)			patients	Male [ <i>n</i> (%)]	Female [ <i>n</i> (%)]	age (IQR), mean±SD	NIHSS score mean (SD)	baseline CT mean (SD)	carotid artery occlusion [ <i>n</i> (%)]	middle cerebral artery occlusion [ <i>n</i> (%)]	middle cerebral artery occlusion [ <i>n</i> (%)]
Berkhermer (2015) [13]	Netherlands	RCT	MM: 267 EVT + MM: 233	MM: 157 (58.8) EVT + MM: 135 (57.9)	MM: 110 (41.2) EVT + MM: 98 (42.1)	MM: 65.7 EVT+MM: 65.8	MM: 18 (14–22) EVT+MM: 17 (14–21)	MM: 9 (8–10) EVT+MM: 9 (7–10)	MM: 75/266 (28.2) EVT+MM: 59/233 (25.3)	MM: 165/266 (62.0) EVT+MM: 154/233 (66.1)	MM: 21/266 (7.9) EVT+MM: 18/233 (7.7)
(2016) [8]	France	RCT	MM: 208 EVT + MM: 204	MM: 104 (50) EVT+MM: 116 (57)	MM: 104 (50) EVT+MM: 88 (43)	MM: 68 (54-75) EVT+ MM: 66 (54-74)	MM: 17 (13–20) EVT+MM: 18 (15–21)	MM: 0-4 (35 [17%]), 5-7 (52 [26%]), 8-10 (115 [57%]) EVT+ MM: 0-4 (21 [19%]), 5-7 (80 [41%]), 8-10 (94 [48%])	MM: 24 (12) EVT + MM: 24 (12)	MM: 164 (79) EVT + MM: 176 (86)	MM: 2 (1) EVT+MM: 0
Campbell (2015) [4]	Australia, New Zealand	RCT	MM: 35 EVT + MM: 35	MM: 17 (49) EVT + MM: 17 (49)	MM: 18 (51) EVT + MM: 18 (51)	MM: 70.2 ± 11.8 EVT + MM: 68.6 ± 12.3	MM: 13 (9–19) EVT+MM: 17 (13–20)	NR	MM: 11 (31) EVT + MM: 11 (31)	MM: 18 (51) EVT + MM: 20 (57)	MM: 6 (17) EVT + MM: 4 (11)
Goyal (2015) [11]	Worldwide	RCT	MM: 150 EVT + MM: 165	MM: 71 (47.3) EVT + MM: 79 (47.9)	MM: 79 (52.7) EVT + MM: 86 (52.1)	MM: 70 EVT + MM: 71	MM:17 EVT + MM: 16	MM: 9 (8–10) EVT+MM: 9 (8–10)	MM: 39/147 (26.5) EVT+MM: 45/163 (27.6)	MM: 105/147 (71.4) EVT+MM: 111/163 (68.1)	MM: 3/147 (2.0) EVT+MM: 6/163 (3.7)
Jovin (2015) [10]	Spain	RCT	MM: 103 EVT + MM: 103	MM: 54 (52:4) EVT + MM: 55 (53:4)	MM: 49 (47.6) EVT + MM: 48 (46.6)	MM: 67.2 ± 9.5 EVT + MM: 65.7 ± 11.3	MM: 17.0 (12.0–19.0) EVT+MM: 17.0 (14.0–20.0)	MM: 8.0 (6.0–9.0) EVT+MM: 7.0 (6.0–9.0)	MM: 27/101 (26.7) EVT + MM: 26/102 (25.5)	MM: 26/102 (25.5) EVT + MM: 66/102 (64.7)	MM: 8/101 (7.9) EVT+MM: 10/102 (9.8)
Saver (2015) [12]	Worldwide	RCT	MM: 98 EVT + MM: 98	MM: 45/96 (47) EVT + MM: 54/98 (55)	MM: 51/96 (53) EVT + MM: 44/98 (45)	MM: 66.3 ± 11.3 EVT + MM: 65.0 ± 12.5	MM: 17 EVT + MM: 17	MM: 9 EVT+MM: 9	MM: 15/94 (16) EVT+MM: 17/93 (18)	MM: 72/94 (77) EVT+MM: 62/93 (67)	MM: 6/94 (6) EVT + MM: 13/93 (14)
NR Not reported,	ASPECT Alberta str	oke programme e	arly CT score, <i>RCT</i>	Randomized contr	olled trial, USA Uni	ted States of Ame	rica, <i>UK</i> United King	Jdom, <i>EVT</i> +MM er	ndovascular throm	bectomy plus mec	lical treatment,

<sup>a</sup> All middle-cerebral-artery occlusions involved the M1 segment, except in one patient in the medical-therapy group who had an occlusion involving the M2 segment MM Medical treatment, /QR Interquartile range, NIHSS National institute health stroke scale, SD Standard deviation

Table 1 (continued)

					Odds Rat		Odd3 Ratio
	Study or Subgroup	log[Odds Rati	o] SE	Weight	IV, Random,	95% CI	IV, Random, 95% CI
	Albers, 2018	1.211	0.275	6.2%	3.36 [1.96	, 5.76]	
	Bendszus, 2023	0.94	B 0 1644	10.3%	1.67 [1.00	2 301	
	Bracard, 2015	0.329	0 1731	9.9%	1.39 (0.99	1.951	
	Campbell, 2015	0.741	9 0.2855	5.9%	2.10 [1.20	3.671	
	Goyal, 2015	1.131	4 0.2236	7.9%	3.10 [2.00	4.80]	
	Huo, 2023	0.314	8 0.1074	13.0%	1.37 [1.11	1.69]	
А	Jovin, 2015	0.530	06 0.2458	7.1%	1.70 [1.05	, 2.75]	·
	Mocco, 2016	0.587	8 0.3768	4.0%	1.80 [0.86	, 3.77]	
	Murl, 2016	0.951	7 0.5226	2.4%	2.59 [0.93	, 7.21]	
	Nogueira, 2018	0.693	0.2606	6.6%	2.00 [1.20	, 3.33]	
	Sarraj, 2023	0.412	21 0.1172	12.6%	1.51 [1.20	, 1.90]	
	Yoshimura, 2022	0.883	0.2578	6.7%	2.42 [1.46	, 4.01]	
	Total (95% CI)			100.0%	1.91 [1.6]	2.261	▲
	Heterogeneity: Tau <sup>2</sup> =	0.05: Cht <sup>2</sup> = 20	6.11. df = 1	2 (P = 0.	01): 12 = 54%		
	Test for overall effect:	Z = 7.38 (P < 0	0.00001)		v.,, · · · · · ·	0.	2 0.5 1 2 5
							Favours [MI] Favours [EVI + MI]
	· · · · · ·		.)		Odds Rat	10	Odds Ratio
	Study or Subgroup	log[Odds Rati	0] SE	Weight	IV, Random,	95% CI	IV, Random, 95% CI
	Berkhemer, 2015	0.72	5 0.3386	54.7%	2.07 [1.07	, 4.02]	
	Campbell, 2015	0.87	0.5161	23.5%	2.40 [0.87	, 6.60]	
B	Muri, 2016	2.034	0.8086	9.6%	7.63 [1.56,	37.22]	
-	rosnimura, 2022	0.530	0.717	12.2%	1.70 [0.42	, 6.93]	
	Total (95% CI)			100.0%	2 37 [1 49	3 871	
	Heteropenetto Tau? -	0.00. Chi - 2	47 df - 3	/P - 0 48	2.57 [1.4.	, 5.67]	
	Test for overall effect:	7 = 3 45 (P = 1	0006)	(r = 0.40		0.0	5 0.2 1 5 20
	rest for overall effect.	2 - 3.43 (r - 0					Favours [MT] Favours [EVT+MT]
					Odds Rat	io	Odds Ratio
	Study or Subgroup	log[Odds Rati	o] SE	Weight	IV, Random,	95% CI	IV, Random, 95% CI
	Albers, 2018	0.982	21 0.2613	7.5%	2.67 [1.60	, 4.46]	
	Bendszus, 2023	1.968	0.621	2.1%	7.16 [2.12,	24.18]	
	Berkhemer, 2015	0.770	0.2249	8.8%	2.16 [1.39	, 3.36]	
	Bracard, 2015	0.438	33 0.1987	9.8%	1.55 [1.05	, 2.29]	
	Campbell, 2015	1.435	0.5605	2.5%	4.20 [1.40,	12.60]	
	Goyal, 2015	0.530	06 0.1369	12.6%	1.70 [1.30	, 2.22]	
	Hup, 2023	0.963	12 0.2237	8.8%	2.62 [1.69	4.06]	
С	Jovin, 2015	0.741	9 0.3299	5.7%	2.10 [1.10	, 4.01]	
-	Khoury, 2017	0.495	9 0.465	3.4%	1.64 [0.66	, 4.08]	
	Mocco, 2016	0.336	65 0.4323	3.8%	1.40 [0.60	, 3.27]	
	Murl, 2016	0.751	4 0.6051	2.2%	2.12 [0.65	6.94]	
	Nogueira, 2018	1.833	33 0.3549	5.1%	6.25 [3.12,	12.54]	
	Sarraj, 2023	1.088	86 0.3156	6.0%	2.97 [1.60	, 5.51]	
	Saver, 2015	0.530	6 0.1651	11.3%	1.70 [1.23	, 2.35]	
	Yoshimura, 2022	0.582	22 0.1914	10.1%	1.79 [1.23	, 2.60]	
	Total (95% CI)			100.0%	2.19 [1.8]	, 2.64]	•
	Heterogeneity: Tau <sup>2</sup> =	0.06; Chl <sup>2</sup> = 2	5.86, df = 1	14 (P = 0.	03); F = 46%	0.05	0 2 1 5 20
	Test for overall effect:	Z = 8.10 (P < 0	0.00001)			0.05	Eavours (MT) Eavours (EVT+MT)
							Favours (MT) Favours (EVT+MT)
		EVT + MT	MT		Odde	Ratio	Odds Ratio
		EVI + MI			Ouus		
	Study or Subgroup	Events Total	Events T	otal We	ght IV, Rand	om, 95% CI	IV, Random, 95% CI
	Study or Subgroup Bendszus, 2023	Events Total 39 124	Events T	otal We	ght IV, Rand	om, 95% CI 1.59, 5.81]	IV, Random, 95% CI
	Study or Subgroup Bendszus, 2023 Berkhemer, 2015	Events Total 39 124 119 233	Events T 16 95	otal Wei 122 10 267 32	ght IV, Rando .7% 3.04 [ .7% 1.89 ]	om, 95% Cl 1.59, 5.81] 1.32, 2.71]	IV, Random, 95% CI
	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023	Events Total 39 124 119 233 108 230	Events T 16 95 75	otal Wei 122 10 267 32 225 29	ght IV, Rand .7% 3.04 [ .7% 1.89 [ .5% 1.77 [	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023	Events Total 39 124 119 233 108 230 67 177	Events T 16 95 75 32	otal We 122 10 267 32 225 29 171 16	ght IV, Rand 1.7% 3.04 [ 1.7% 1.89 [ 1.5% 1.77 [ 1.3% 2.65 [	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022	Events Total 39 124 119 233 108 230 67 177 31 100	Events T 16 95 75 32 13	otal We 122 10 267 32 225 29 171 16 102 6	iv, Rand           iv, Rand <t< td=""><td>om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32]</td><td>IV, Random, 95% CI</td></t<>	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022	Events Total 39 124 119 233 108 230 67 177 31 100	Events T 16 95 75 32 13	otal         Wei           122         10           267         32           225         29           171         16           102         6	(ght IV, Rand 1.7% 3.04 [ 1.7% 1.89 [ 1.5% 1.77 [ 1.3% 2.65 [ 1.7% 3.08 [	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% Cl)	Events Total 39 124 119 233 108 230 67 177 31 100 864	Events T 16 95 75 32 13	otal         We           122         10           267         32           225         29           171         16           102         6           887         100	ght         IV, Randi           0.7%         3.04 [           .7%         1.89 [           .5%         1.77 [           .3%         2.65 [           .7%         3.08 [	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69]	IV, Random, 95% Cl
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events	Events Total 39 124 119 233 108 230 67 177 31 100 864 364	Events T 16 95 75 32 13 231	otal         We           122         10           267         32           225         29           171         16           102         6           887         100	ght         IV, Randi           0.7%         3.04 [           .7%         1.69 [           .5%         1.77 [           .3%         2.65 [           .7%         3.08 [           0.0%         2.17 [	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69]	IV, Random, 95% Cl
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% Cl) Total events Heterogenety: Tau <sup>2</sup> =	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4	Events T 16 95 75 32 13 231 24, df = 4	otal         Wei           122         10           267         32           225         29           171         16           102         6           887         100           (P = 0.37	ght IV, Rand .7% 3.04 [ .7% 1.89 [ .5% 1.77 [ .3% 2.65 [ .7% 3.08 [ 0.0% 2.17] ); t <sup>2</sup> = 6%	om, 95% CI 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69]	IV, Random, 95% Cl
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < 0	Events T 16 95 75 32 13 231 24, df = 4 0.00001)	otal         Wei           122         10           267         32           225         29           171         16           102         6           887         100           (P = 0.37)	ght IV, Rand 1.7% 3.04 [ 1.7% 1.89 [ 1.5% 1.77 [ 1.3% 2.65 [ 1.7% 3.08 [ 0.0% 2.17] ); i <sup>2</sup> = 6%	om, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> = Test for overall effect:	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 • 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < 0	Events T 16 95 75 32 13 231 24, df = 4 0.00001)	otal         We           122         10           267         32           225         25           171         16           102         8           887         100           (P = 0.37)	ght IV, Rand .7% 3.04 [ .7% 1.89 [ .5% 1.77 [ .3% 2.65 [ .7% 3.08 [ .0% 2.17 ] ); i <sup>2</sup> = 6%	om, 95% CI 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect:	Events Total 39 124 119 233 108 230 67 177 31 100 864 .0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < (	Events T 16 95 75 32 13 231 24, df = 4 0.00001)	otal         We           122         10           267         32           225         29           171         16           102         6           887         100           (P = 0.37	ght IV, Rand .7% 3.04 [ .7% 1.89 ] .5% 1.77 [ .5% 1.77 3.08 ] .7% 3.08 [ .0% 2.17 ] .1° – 6% Odds ra	om, 95% CI 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < (	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V	otal Wei 122 10 267 32 225 25 171 16 102 6 887 100 (P = 0.37 Weight	lght IV, Rand .7% 3.04 [ .7% 1.88 ] .5% 1.77 [ .5% 1.77 3.08 ] .7% 3.08 [ .0% 2.17 ] .0% 2.17 ] .0% 2.17 ] .0% 2.17 ]	om, 95% CI 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 .0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR]	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V	otal         Wei           122         10           267         32           225         25           171         16           102         8           887         100           (P = 0.37           Weight	ght IV, Rand .7% 3.04 [ .7% 1.89 ] .5% 1.77 [ .3% 2.65 ] .7% 3.08 [ .0% 2.17 ] ); <sup>2</sup> = 6% Odds ra	om, 95% CI 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% CI
D	Study or Subgroup       Bendszus, 2023       Berkhemer, 2015       Huo, 2023       Sarraj, 2023       Yoshimura, 2022       Total (95% Cl)       Total events       Heterogeneity: Tau <sup>2</sup> –       Test for overall effect:       Study or Subgroup       Berkhemer, 2015	Events Total 39 124 119 233 108 230 67 177 31 100 864 • 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR] 0.8329	Events T 16 95 75 32 13 24, df = 4 0.00001) SE V 0.425	otal         Wei           122         10           267         32           225         25           171         16           102         8           887         100           (P = 0.37)           Weight           8.4%	ght IV, Rand .7% 3.04 [ .7% 1.69 [ .7% 1.69 [ .7% 3.08 [ .7% 3.08 [ .0% 2.17] ); P = 6% Odds ra IV, Random, 2.30 [1.0	bm, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenetly: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell. 2015	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 • 0.00; Ch <sup>2</sup> - 4. Z = 7.02 (P < ( p log[OR] 0.8329 1.7918	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605	otal         Wei           122         10           267         32           225         25           171         16           102         6           887         100           (P = 0.37           Weight         8.4%           5.5%	ght IV, Rand .7% 3.04 [ .7% 3.04 [ .7% 1.89 ] .5% 1.77 [ .3% 2.65 ] .7% 3.08 [ .7% 3.08 [ .7% 3.08 ] .7% 3.08 [ .7%	bm, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% Cl
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605 0.1501	otal         Wei           122         10           267         32           225         29           101         10           102         8           (P = 0.37)           Weight           8.4%           5.5%           23.0%	ght IV, Rand .7% 3.04 [ .7% 1.68] .5% 1.77 [ .5% 1.77 [ .5% 2.65 [ .7% 3.08 [ 0.0% 2.17 ] ); i <sup>2</sup> = 6% Odds ra IV, Random, 2.30 [1.0 6.00 [2.00]	bm, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.175, 2.69] tito 95% Cl 00, 5.29] 0, 18.00] 00, 5.61]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> = Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015	Events Total 39 124 119 234 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605 0.1591	otal         Wei           122         10           267         32           225         25           101         10           887         100           (P = 0.37           Weight         8.4%           5.5%         23.0%	ght IV, Rand .7% 3.04 [ .5% 1.89 [ .5% 1.87 [ .5% 1.77 [ .3% 2.65 [ .0% 2.17 ] .0%	Dem, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 	IV, Random, 95% CI
F	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605 0.5591 0.6171	otal         Wei           122         10           267         32           225         25           171         16           102         6           887         100           (P = 0.37)           Weight           8.4%           5.5%           23.0%           4.6%	ght IV, Rand .7% 3.04 [ .5% 1.87 [ .5% 1.77 [ .5% 2.17] .3% 2.65 [ .7% 3.08 [ .7% 3.08 [ .0% 2.17] .3% 2.65 [ .7% 3.08 [ .0% 2.17] .3% 2.65 [ .3% 2.	bm, 95% Cl 1.59, 5.81] 1.32, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] tio 95% Cl 0, 5.29] 0, 18.00] 0, 5.80] 0, 5.83]	IV, Random, 95% CI
D	Study or Subgroup           Bendszus, 2023           Berkhemer, 2015           Huo, 2023           Sarral, 2022           Total (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> –           Test for overall effect:           Study or Subgrouu           Berkhemer, 2015           Gangal, 2015           Huo, 2023           Jovin, 2015	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4. z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047	Events         T           16         95           75         32           13         231           24, df = 4         0.00001)           SE         V           0.425         0.5605           0.5605         0.6171           0.3266         0.3266	otal         Wei           122         10           267         32           225         29           101         10           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%	ght IV, Rand 77% 3.04 [ 77% 3.04 [ 77% 3.04 [ 55% 1.77 [ 1.5% 3.04 [ 1.77 3.	m, 95% Cl 1.59, 5.81] 1.52, 2.71] 1.21, 2.59] 1.21, 2.59] 1.22, 2.59] (1.75, 2.69] (1.75, 2.6	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605 0.1591 0.6171 0.3266 0.6227	otal         Wei           122         10           267         32           225         225           102         8           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%	ght IV, Rand 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.08 [ 1,7	m, 95% C1 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] witho 95% C1 0, 5.29] 0, 18.00] 0, 18.00] 0, 18.03] 4, 14.38] , 10.43] 4, 6, 201	IV, Random, 95% Cl
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Muri, 2016	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0966	Events T 16 95 32 231 24, df - 4 0.00001) SE V 0.425 0.5605 0.6171 0.3266 0.6227 0.2666	otal         Wei           122         10           267         32           225         25           171         18           102         6           887         100           (P = 0.37)         8.4%           5.5%         23.0%           4.6%         12.1%           4.6%         19.3%	ght IV, Rand 7.7% 3.04 [ 7.7% 3.04 [ 7.7% 1.89 [ 5.5% 1.77 [ 3.06 [ 5.5% 1.77 ] 7.7% 3.08 [ 1.3% 2.65 [ 5.5% 2.17 ] 7.7% 3.08 [ 0.0% 2.17 ] 7.8% 3.08 [ 0.0% 2.17 ] 7.9% 3.08 [ 0.0% 2.17 ] 7.8% 3.08 [ 0.0% 2.1	0m, 95% Cl 1.59, 5.81] 1.52, 2.71] 1.21, 2.59] 1.22, 2.59] 1.24, 2.59] 1.24, 2.59] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 95% Cl 00, 5.29] 1, 18.00] 10, 5.29] 1, 18.00] 10, 5.60] 5, 14.38] 0, 10.43] 44, 6.20] 10, 46.00]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018	Events Total 39 124 119 233 108 230 67 127 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.0257	Events T 16 95 75 32 13 24, df = 4 .00001) SE V 0.425 0.5605 0.1591 0.6126 0.3266 0.3266 0.3266 0.3266	otal         Wei           122         10           267         32           225         25           101         10           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%           19.3%	ght IV, Rand 177 3.0.4 [ 178 3.0.4 [ 177 3.0.4 ] 158 1.77 1.88 [ 158 1.77 3.08 [ 1.78 3.08 [ 1.77 3.08 [ 1.78 3.08 [ 1.77 3.08 [ 1.78 3.08 [ 1.77 3.08	m, 95% C1 1.59, 5, 81] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] without the second secon	IV, Random, 95% CI
D	Study or Subgroup           Bendszus, 2023           Berkhemer, 2015           Huo, 2023           Sarraj, 2023           Yoshimura, 2022           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> – Test for overall effect:           Study or Subgrou           Berkhemer, 2015           Goyal, 2015           Huo, 2023           Jovin, 2015           Muri, 2016           Nogueira, 2018           Sarraj, 2023	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 0.0853	Events         T           16         95           95         75           32         13           24, df = 4         4           0.00001)         SE         V           0.425         0.5605         0.15605           0.6171         0.3266         0.6277           0.2069         0.3366	otal         Wei           122         10           267         32           225         25           101         18           102         6           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%           19.3%           11.6%	ght IV, Rand 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.08 [ 1,5% 1,77 ] 3,8% 2.65 [ 1,5% 3.08 [ 1,0% 2.17 ] 1,7% 3.08 [ 1,0% 2.17 ] 1,0% 2.17 ] 1,0	m, 95% C1 1.59, 5.81] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 95% C1 100, 5.29] 0, 18.00] 100, 5.60] 1, 14.38] 0, 10.43] 14, 6.20] 10, 4.50] 6, 2.84]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenetly: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Nuuri, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> - 4. z - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556	Events T 16 95 75 32 13 231 24, df = 4 0.00001) SE V 0.425 0.5605 0.1591 0.6171 0.3266 0.3266 0.3266 0.3326	otal         Wei           122         10           267         32           225         25           102         8           1102         8           887         100           (P = 0.37           Weight         8.4%           5.5%         23.0%           4.6%         12.1%           4.6%         11.6%           11.0%         11.0%	ght V, Rand 77% 3.04 [ 77%	m, 95% C1 1.59, 5, 81] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] with 95% C1 00, 5.29] 0, 18.00] 00, 5.60] 1, 14.38] 00, 5.60] 1, 14.38] 00, 10, 43, 44 1, 6.20] 10, 4.50] 6, 2.84] 6, 7.00]	IV, Random, 95% CI
D	Study or Subgroup           Bendszus, 2023           Berkhemer, 2015           Huo, 2023           Sarraj, 2023           Yoshimura, 2022           Total (95% CI)           Total events           Heterogenety: Tau <sup>2</sup> – Test for overall effect:           Study or Subgrou           Berkhemer, 2015           Goyal, 2015           Huo, 2023           Jovin, 2015           Muri, 2016           Nogueira, 2018           Sarraj, 2023           Yoshimura, 2022	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556	Events         T           16         95           75         32           13         231           24, df = 4         .000001)           SE         V           0.425         0.5605           0.1591         0.61711           0.3266         0.2069           0.3366         0.3522	otal         Wei           122         10           267         32           225         25           102         8           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%           19.3%           11.6%           11.0%	ght IV, Randor 1778 3.04 [ 1778 3.04 [ 1778 1.89 [ 1558 1.77 ] 1558 1.77 [ 1558 1.77 ] 1558 1.77 3.08 [ 1558 1.77 3.08 [ 1558 1.77 3.08 [ 1578 3.08 [ 177 3.08 [	m, 95% C1 1.59, 5, 61] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] 4.175, 2.69] 95% C1 10, 5, 29] 0, 18.00] 10, 5, 629] 0, 18.00] 10, 5, 629] 1, 14.38] 1, 10, 43] 4, 6, 20] 10, 4, 50] 6, 2, 84] 6, 7, 00]	IV, Random, 95% CI
D	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4. z = 7.02 (P < C p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.2556	Events         T           16         95           95         75           32         13           241         df = 4           2,00001)         SE           0.425         0.5605           0.5605         0.6171           0.6227         0.2366           0.3366         0.33522	otal         Wei           122         10           267         32           225         25           102         8           102         8           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%           19.3%           11.6%           11.0%           100.0%	ght IV, Rand 77% 3.04 [ 77%	m, 95% Cl 1.59, 5.81] 1.52, 2.71] 1.21, 2.59] 1.22, 2.59] 1.24, 2.59] 1.24, 2.59] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 95% Cl 00, 5.29] 0, 18.00] 00, 5.60] 5, 14.38] 0, 10.43] 44, 6.20] 10, 4.50] 76, 2.84] 74, 4.341	IV, Random, 95% CI
D	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Gampbell, 2015 Gaoyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556	Events T 16 95 75 32 13 24, df = 4 0.00001) SE V 0.425 0.5605 0.1591 0.6171 0.3266 0.6227 0.2069 0.3366 0.3522	otal         Wei           122         10           267         32           252         25           171         16           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           11.6%           11.0%           100.0%	ght IV, Randor 1778 3.04 [ 1778 3.04 [ 1778 3.04 [ 1778 1.85] 1.5% 1.77 [ 1.5% 1.77 ] 1.7% 3.08 [ 1.7% 3.08 [ 1.	m, 95% C1 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] where the set of th	IV, Random, 95% CI
E	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Goyal, 2015 Muri, 2016 Muri, 2016 Muri, 2016 Muri, 2018 Sarraj, 2023 Yoshimura, 2022 Total	Events         Total           39         124           139         124           119         230           67         177           31         100           864         0.00; Ch² = 4.           0.00; Ch² = 4.         Z = 7.02 (P < (P < 0)	Events         T           16         95           95         75           32         13           24, df = 4         4           0.00001)         SE         V           0.425         0.5605         0.15605           0.6171         0.3266         0.6277           0.2069         0.33666         0.3522	otal         Wei           122         10           267         32           225         25           171         18           887         100           (P = 0.37           Weight           8.4%           5.5%           23.0%           4.6%           12.1%           4.6%           19.3%           11.6%           11.0%	ght IV, Rand 7.7% 3.04 [ 7.7% 3.04 [ 7.7% 3.04 [ 7.7% 3.04 [ 7.7% 3.08 [ 7.7% 3.08 [ 1.3% 2.65 ] 7.7% 3.08 [ 1.3% 2.65 ] 7.7% 3.08 [ 1.3% 2.65 ] 7.7% 3.08 [ 1.3% 2.65 ] 7.7% 3.08 [ 7.7% 3.08 [ 7.7	m, 95% C1 1.59, 5.61] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] (1.75, 2.69] 95% C1 100, 5.29] 0, 18.00] 100, 5.60] 1, 14.38] 0, 10.43] 14, 6.20] 10, 4.50] 6, 2.84] 76, 2.84] 76, 7.00] 77, 4.34]	IV, Random, 95% CI
E	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Gampbell, 2015 Gaoyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effet	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P	Events         T           16         95           95         75           32         13           24, df = 4         .00001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.3522           < 0.00001	otal         Wei           122         10           124         102           171         11           1887         100           8887         100           8887         100           8887         100           84%         5.5%           23.0%         4.6%           19.3%         11.6%           11.0%         100.0%	ght IV, Randor 1778 3.04 [ 1778 3.04 [ 1778 1.88] 1.58 1.77 [ 1.58 1.77 ] 1.58 1.77 3.08 [ 1.58 1.77 3.08 [ 1.78 3.08 [ 1.77 3.08 [ 1.78 3.08 [ 1.77 3.08 [ 1.78 3.08 [ 1.77	om, 95% C1           1.59, 5, 81]           1.52, 2, 71]           1.21, 2.59]           1.62, 4, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 6, 32]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]           1.50, 7, 1.30]	IV, Random, 95% CI
E	Study or Subgroup       Bendszus, 2023       Berkhemer, 2015       Huo, 2023       Sarraj, 2023       Yoshimura, 2022       Total (95% CI)       Total events       Heterogenetiy: Tau <sup>2</sup> –       Test for overall effect:       Study or Subgrou       Berkhemer, 2015       Goyal, 2015       Muri, 2015       Muri, 2015       Nogueira, 2018       Sarraj, 2023       Yoshimura, 2022       Total       Test for overall effer       Test for overall effer	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P	Events         T           16         95           95         75           32         13           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.61711           0.3266         0.3266           0.2069         0.33666           0.3522            < 0.00001	otal         Wei           122         10           124         12           125         22           225         22           1102         8           887         100           (P = 0.37           Weight         8.4%           5.5%         23.0%           12.1%         4.6%           12.1%         4.6%           19.3%         11.6%           11.0%         100.0%	ght IV, Rand 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 3.04 [ 1,7% 1.89 [ 1,5% 1.77 [ 3,08 [ 1,7% 3.08 [ 1,7% 3.0	m, 95% C1 1.59, 5.61] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 95% C1 00, 5.69] 0, 16.00] 10, 5.69] 0, 14.38] 0, 10.43] 4, 6.20] 10, 4.50] 6, 2.84] 7, 4.34]	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenetty: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Murl, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup of Heterogenetry: Tau	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P ifferences: NO	Events T 16 95 75 32 13 24, df = 4 .000001) SE 0.425 0.5605 0.1591 0.6171 0.3266 0.3266 0.3262 < 0.00001 classes < 0.00001 classes < 0.00001 classes < 0.00001 classes < 0.00001 classes < 0.00001 classes < 0.00001 classes < 0.1591 0.3266 0.3266 0.3262 < 0.3562 < 0.3562 < 0.3562 < 0.3562 < 0.3565 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3266 0.3552 0.3266 0.3552 0.3266 0.3552 0.3266 0.3552 0.3266 0.3552 0.3266 0.3552 0.3266 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3555 0.3552 0.3552 0.3552 0.3552 0.3552 0.3552 0.3555 0.3555	otal         Wei           122         11           124         12           125         22           225         23           225         100           (P = 0.37)           Weight           8.84%           4.6%           12.1%           14.6%           11.0%           100.0%	ght IV, Rand 177 3.04 [ 178 3.04 [ 178 3.04 [ 178 3.04 [ 158 1.77 1.8] 158 1.77 3.08 [ 158 1.77 3.08 [ 00dds ra V, Random, 2.30 [1.0 do 0.00 [2.0 0.0 do 4.10 [0.0 0.0 do 4.10 [0.0 0.0 do 4.10 [0.0 do 1.83 [0.0 d	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] with 95% C1 95% C1 95% C1 95% C1 90, 5.29] 9, 18.00] 10, 5.60] 10, 16.43] 14, 6.20] 16, 7, 00] 17, 4.34] %	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effect Test for subgroup d Heterogeneity: Tau	Events Total 39 124 119 233 108 230 67 177 31 100 864 0.00; Ch <sup>2</sup> = 4. z = 7.02 ( $P < C$ p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.2556 ct: Z = 8.27 (P lifferences: No z = 0.06; Ch <sup>2</sup> = 2	Events         T           16         95           75         32           13         231           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.3522           < 0.00001	otal         Wei           122         10           225         227           225         227           225         227           225         227           111         112           102         6           5.5%         23.0%           4.6%         5.5%           12.1%         4.6%           19.3%         11.6%           11.0%         6           6         6           9.3%         11.0%           00.0%         1)	ght         IV, Random           1.78         3.04 [           1.78         1.89 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           3.08 [         5.5% [           0.05 [         2.47 [           0.11 [         - 6%           Odds ra         1.03 [           2.30 [1.0 [         1.0 [           3.00 [2.0 [         1.0 [           1.42 [         1.28 [           3.00 [2.0 [         1.0 [           3.00 [2.1 [         1.7 [           3.01 [2.1 [         1.47 [           3.02 [2.4 [         1.47 [           3.03 [2.4 [         1.47 [           3.04 [2.4 [         1.47 [           3.05 [         1.47 [           3.28 [2.4 [         0.11];   <sup>2</sup> = 35 [	m, 95% C1 1.59, 5.61] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.175, 2.69] 4.175, 2.69] 4.175, 2.69] 4.100, 5.60] 4.14.38] 5.10, 4.30] 10, 5.60] 10, 5.60] 10, 5.60] 10, 5.60] 10, 5.60] 10, 5.60] 14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38] 5.14.38	IV, Random, 95% CI
E	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Starraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Goyal, 2015 Mur, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup of Heterogeneity: Tau	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 0.00; Ch <sup>2</sup> = 4. Z = 7.02 (P < (P	Events         T           16         95           95         75           32         13           24, df = 4         0.00001)           SE         V           0.425         0.5605           0.5605         0.1591           0.6171         0.3266           0.3266         0.33522           < 0.00001	otal         Wei           122         10           225         22           2217         12           101         12           887         100           887         100           887         100           84%         5.5%           23.0%         23.0%           12.1%         4.6%           12.1%         4.6%           11.6%         11.6%           11.6%         11.6%           100.0%         ))           e         8 (P =	ght IV, Rand 7.7% 3.04 [ 7.7% 3.04 [ 7.7% 1.89 [ 5.5% 1.77 [ 3.0% 2.17 ] 3.0% 2.17 ] 3.1	m, 95% C1 1.59, 5, 81] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] with 95% C1 10, 5.29] 0, 18,00] 10, 5.60] 1, 14,38] 1, 10, 4.50] 6, 2.84] 6, 7,00] 7, 4.34] %	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup>	Events Total 39 124 119 233 108 230 67 177 31 100 864 364 2 - 7.02 (P < ( p log[OR] 0.8329 1.7918 0.4312 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P lifferences: No <sup>2</sup> = 0.06; Chl <sup>2</sup> =	Events         T           16         95           95         75           32         13           24, df = 4         .000001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.3522           < 0.00001	otal         Wei           122         10           2247         32           2257         22           2257         22           1102         6           887         100           (P = 0.37)         7           Weight         12.1%           4.6%         19.3%           11.0%         100.0%           ()         e           e = 8 (P =         8 (P =           ttrol         100	ght         V, Rand           1.78         3.04 [           1.78         1.89 [           5.5%         1.77 [           3.08 [         5.5% [           5.5%         1.77 [           3.08 [         5.5% [           V, Random,         2.30 [1.0 (           2.30 [1.0 (         2.17 [           3.00 [2.00 (         4.10 [           4.10 [3.30 [1.1 (         3.00 [2.0 (           4.10 [3.3 (         1.83 [0.0 (           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.00 [2.0 (         1.0 [           3.28 [2.4 (         0.11);   <sup>2</sup> = 35	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] where the second	IV, Random, 95% CI
E	Study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Goyal, 2015 Muri, 2015 Muri, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau	Events Total 39 124 39 124 119 233 108 230 67 177 31 100 864 0.00; Chi <sup>2</sup> = 4. z = 7.02 (P < ( p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P lifferences: No <sup>z</sup> = 0.06; Chi <sup>2</sup> = EVT Events Total	Events         T           16         95           95         75           32         13           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.61711           0.2666         0.3266           0.2069         0.3366           0.3522            < 0.00001	otal         Wei           122         10           124         102           125         225           225         225           1102         8           887         100           887         100           847         5.5%           23.0%         4.6%           12.1%         4.6%           19.3%         11.6%           11.0%         100.0%           00         e           e         e           e         e           trol         Total	ght         IV, Rand           1.78         1.89           1.78         1.89           5.5%         1.77           1.80         5.5%           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           2.30 [1.4         6.00 [2.00           4.29 [1.22         5.50 [2.90           1.83 [0.5         3.00 [2.01           3.00 [2.01         1.83 [0.5           3.00 [2.01         1.83 [0.5           3.00 [2.01         1.83 [0.5           3.00 [2.11, 1.47 [0.1]         3.01 [2.40           3.01 [1.7         3.28 [2.40           0.111); 1 <sup>2</sup> = 35         3.00           Weight IV, R         1.47 [0.1]	m, 95% C1 1.59, 5.61] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 95% C1 00, 5.69] 00, 5.69] 00, 5.69] 00, 5.69] 00, 5.69] 00, 5.69] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.53] 17, 4.34] % Dodds ratio andom, 95% 0	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Gampbell, 2015 Gayal, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup of Heterogeneity: Tau <sup>2</sup>	Events Total Sector 2 = 8.27 (P Events Total Berlin Control (C)	Events         T           16         95           95         75           32         13           24, df = 4         .000001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.33522           < 0.00001	otal         Wei           122         10           2267         32           2250         22           2250         22           111         11           102         6           8887         100           (P = 0.37)           Weight           8.4%           5.23.0%           4.6%           12.1%           4.6%           19.3%           11.0%           100.0%           e           e           e           e           e           e           e           e           for           100.0%	ght         IV, Rand           1.78         3.04 [           1.78         1.88 [           1.5%         1.81 [           1.5%         1.77 [           3.08 [         1.87 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           0.10 [3.30 [         1.07 [           1.03 [0.01 [         1.08 [           3.00 [2.01 [         1.83 [           3.00 [2.01 [         1.83 [           3.00 [2.01 ]         1.83 [           3.00 [2.01 ]         1.83 [           3.00 [2.01 ]         1.83 [           3.00 [2.01 ]         1.83 [           3.00 [2.01 ]         1.83 [           3.00 [2.01 ]         1.83 [           3.28 [         2.4           0.11); I <sup>2</sup> = 38         3.00 [           Weight         IV, R	om, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4, 32] 1.50, 6, 32] 1.75, 2.69] where the second sec	IV, Random, 95% CI
E	Study or Subgroup       Bendszus, 2023       Berkhemer, 2015       Huo, 2023       Sarraj, 2023       Yoshimura, 2022       Total (95% CI)       Total events       Heterogeneity: Tau <sup>2</sup> – Test for overall effect:       Study or Subgrou       Berkhemer, 2015       Goyal, 2015       Muri, 2016       Nogueira, 2018       Sarraj, 2023       Yoshimura, 2022       Total       Test for overall effer       Test for subgroup d       Heterogeneity: Tau <sup>2</sup> Study or Subgroup       Berkhemer, 2015	Events         Total           39         124           39         124           119         233           108         230           67         177           31         100           864         0.00; Chi <sup>2</sup> = 4. $z = 7.02$ ( $P < C$ $p$ log[OR]           0.8329           1.7918           1.411           1.4563           1.7047           0.6043           0.3853           1.2556           ct: Z = 8.27 (P           et viewerts           Total           9           2           9.06; Chi <sup>2</sup> =           9           2           9           2           20.06; Chi <sup>2</sup> =           9           9           9	Events         T           16         95           75         32           13         24, df = 4           2,00001)         SE         V           0.425         0.5605         0.1591           0.6171         0.3266         0.3266           0.2069         0.3366         0.3522           < 0.00001	otal         Wei           122         10           2247         32           2257         22           2257         22           2257         22           887         100           (P = 0.37           Weight         8.4%           5.5%         23.0%           23.0%         4.6%           12.1%         4.6%           19.3%         11.6%           11.0%         100.0%           ())         e           e         R (P =           trol         Total	ght IV, Rand 177 3.04 [ 178 3.04 [ 178 3.04 [ 178 3.04 [ 158 1.77 3.08 [ 158 1.77 3.08 [ 158 1.77 3.08 [ 158 1.77 3.08 [ 158 2.65 1 178 3.08 [ 178 3.08 [ 178 3.08 [ 178 3.08 [ 178 3.08 [ 178 3.08 [ 179 3.08	m, 95% C1 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 4.162, 4.32] 1.75, 2.69] 95% C1 10, 5, 2.69] 0, 5, 2.69] 0, 18, 00] 10, 5, 5, 29] 0, 18, 00] 10, 5, 5, 29] 1, 14, 38] 1, 10, 43, 50] 10, 4, 50] 10, 4, 50] 10, 4, 50] 17, 4, 34] % Odds ratio andom, 95% C 2.01 [1, 37, 2, 5]	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau' Study or Subgroup Berkhemer, 2015 Goval, 2015	Events Total Sector 2 (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	Events         T           16         95           95         75           32         13           24, df = 4         0.00001)           SE         0.425           0.5605         0.1591           0.6171         0.3266           0.6227         0.2069           0.3566         0.3552           < 0.00001	otal         Wei           122         10           225         22           225         100           (P = 0.37)           Weight           8.4%           5.23.0%           4.6%           12.1%           14.6%           11.0%           e           = 8 (P =           trol           Total           245	ght         IV, Rand           1.78         3.04 [           1.78         1.88 [           1.58         1.77 [           3.08 [         5.5% [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           0.07         2.17 ]           1.77         3.08 [           0.07         2.17 ]           1.77         5.00 [2.00 ]           4.10 [3.3         3.00 [2.00 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.01 [2.01 ]           1.83 [0.3]         3.01 [2.01 ]           1.83 [0.3]         3.01 [2.01 ] <tr< td=""><td>m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4, 32] 1.75, 2.69] without the second se</td><td>IV, Random, 95% CI</td></tr<>	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4, 32] 1.75, 2.69] without the second se	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup> Study or Subgroup Berkhemer, 2015 Goyal, 2015	Events Total Sector 2 (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	Events         T           16         95           95         75           32         13           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.3522           < 0.00001	otal         Wei           122         10           2247         32           2257         22           2257         22           2257         22           887         100           (P = 0.37           Weight         8.4%           5.5%         23.0%           4.6%         12.1%           4.6%         11.0%           100.0%         11.0%           0)         0           0         = 8 (P =           trol         Total           2455         146	ght         IV, Random           1.78         3.04 [           1.78         1.89 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           3.08 [         5.5% [           0.0%         2.17 [           ); i* = 6%         Odds re           V.Random,         2.30 [1.0           2.30 [1.0         4.00 [3.3           4.10 [3.3 [1.3]         3.00 [2.0           1.83 [0.5]         3.00 [2.1           3.00 [2.1         1.00 [2.2           1.83 [0.5]         3.00 [2.1           3.00 [2.1         1.01 [3.3]           3.00 [2.1         1.02 [3.20 [2.9]           1.83 [0.5]         3.00 [2.1           3.00 [2.1         1.47 [0.1]           3.01 [2.4         1.01 [1.1]           3.28 [2.4         0.11]; I* = 38           Weight         IV, R           44.4%         34.7%	m, 95% C1 1.59, 5, 61] 1.59, 5, 61] 1.52, 2, 71] 1.21, 2, 59] 1.62, 4, 32] 1.50, 6, 32] 1.50, 6, 32] 1.50, 6, 32] 1.75, 2, 69] 4.100, 5, 60] 4.14, 38] 5.14, 38] 5.	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Murl, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup> Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015	Events         Total           39         124           39         124           119         230           67         177           31         100           864 $0.00$ ; Ch <sup>2</sup> = 4.           0.00; Ch <sup>2</sup> = 4. $Z = 7.02$ (P < 0	Events         T           16         95           95         75           32         13           24, df = 4         0.00001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3262            < 0.00001	otal         Wei           122         10           225         22           225         10           887         100           887         100           847         3.0%           7.1         16           8.4%         5.5%           23.0%         23.0%           12.1%         4.6%           12.1%         4.6%           11.6%         11.6%           11.6%         11.6%           100.0%         )           e         e           etrol         Total           2455         146           87         146	ght IV, Randor 778 3.04 [ 778 3.04 [ 778 1.85 ] 558 1.77 [ 558 1.77 ] 558 1.77 3.08 [ 00 dds ra V, Random, 2.30 [1.0 dds ra V, Random, 2.30 [1.0 dds ra V, Random, 2.30 [1.0 dds ra V, Random, 2.30 [1.0 dds ra 1.33 [1.0 dds ra 1.33 [1.0 dds ra 3.00 [2.0 dds ra 3.00	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] weights of the second s	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup> Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015	Events         Total           39         124           139         124           119         233           108         230           67         177           31         100           864         0.00; Ch <sup>2</sup> = 4.           z = 7.02 (P < 6	Events         T           16         95           95         75           32         13           24, df = 4         4           0.00001)         SE         V           0.425         0.5605         0.1591           0.6171         0.3266         0.3266           0.3266         0.3252            < 0.00001	otal         Wei           122         10           124         3225           225         22           111         11           102         6           887         100           (P = 0.37)           Weight           8.4%           5.5%           4.6%           12.1%           4.6%           12.1%           4.6%           19.3%           11.0%           100.0%           0)           e           e           11.0%           100.0%           10           245           146           72	ght         IV, Random           1.78         3.04 [           1.78         1.89 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           5.5%         1.77 [           3.26 [         1.77 [           0.00 [         2.17 ]           1.81 [0.4 ]         1.00 [           4.10 [         3.00 [           1.40 [         1.83 [0.4 ]           3.00 [         1.83 [0.4 ]           3.00 [         1.47 [           0.11 ]; I <sup>2</sup> = 35         3.28 [           Weight         IV, R           44.4%         34.7%           20.9%         1.00 [	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4, 32] 1.50, 6, 32] 1.50, 6, 32] 1.50, 6, 32] 1.75, 2, 69] where the set of t	IV, Random, 95% CI
D E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Starral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenetly: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneilty: Tau Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015	Events         Total           39         124           39         124           119         233           108         230           67         177           31         100           864         0.00; Chi <sup>2</sup> = 4. $0.00; Chi2 = 4.         2           p         log[OR]           0.8329         1.7918           1.411         1.4563           1.7047         0.6043           0.03853         1.2556           ct: Z = 8.27 (P           e         EVT           Events         Total           99         2           94         11           44         44  $	Events         T           16         95           95         75           32         13           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.2069         0.3366           0.2069         0.3366           0.2069         3.3366           0.2069         0.3366           0.3522         Con           Events         15           15         73           35         49           32         23           50         90	otal         Wei           122         10           124         102           125         22           125         22           1102         8           1102         8           887         100           887         100           847         3           5.5%         23.0%           12.1%         4.6%           12.1%         4.6%           19.3%         11.6%           11.0%         100.0%           e         e           e         e           totol         11.0%           245         146           87         146           87         124           46%         7	ght         IV. Rand           1.77         3.04 [           1.77         3.04 [           1.77         3.04 [           1.77         3.04 [           1.77         3.04 [           1.5%         1.77 [           1.80 [         5.5%           1.77         3.08 [           1.07         2.17 [           3.17         3.08 [           1.08 [         2.17 [           2.30 [1.0         6.00 [2.00 [4.10 [3.00 [2.00 [4.29 [12:45 [5.50 [2.96 [1.83 [0.0 [3.00 [2.0 [3.00 [2.14 [1.47 [0.1 [3.00 [2.14 [1.47 [0.1 [3.15 [1.7 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47 [1.47	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] with 95% C1 00, 5.29] 00, 5.29] 00, 5.60] 5, 14.38] 00, 5.60] 5, 14.38] 10, 16, 20] 10, 4.620] 10, 4.620] 10, 4.620] 10, 4.620] 10, 4.620] 10, 4.62] 10, 4.	IV, Random, 95% CI
E F	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Goyal, 2015 Huo, 2023 Jovin, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup> Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015	Events Total 39 124 39 124 39 124 39 124 119 233 108 230 67 177 31 100 864 364 2 7.02 ( $P < 0$ p log[OR] 0.8329 1.7918 0.8329 1.7918 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 ( $P$ lifferences: No <sup>2</sup> = 0.06; Chl <sup>2</sup> = EVT Events Total 99 2 94 11 47 4 240	Events         T           16         95           95         75           32         13           24, df = 4         .000001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.3266         0.3222           < 0.00001	otal         Wei           122         10           2247         32           2257         22           2257         22           111         11           102         (P = 0.37)           Weight         10           8.4%         5.23.0%           4.6%         19.3%           11.0%         10.0.0%           0)         e           e         8 (P =           troi         Total           245         146           878         478	ght         IV, Random           1.78         3.04 [           1.78         1.88 [           1.5%         1.87 [           5.5%         1.77 [           3.08 [         5.5% [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           0.10 [3.30 [1.0 [           3.00 [2.0 (           1.83 [0.1 [           3.00 [2.0 (           1.83 [0.1 [           3.00 [2.0 (           1.83 [0.1 [           3.00 [2.0 (           1.83 [0.2 [           3.00 [2.0 (           1.83 [0.1 [           3.00 [2.0 (           1.83 [0.1 [           3.28 [2.4 [           0.11); I <sup>2</sup> = 38           Weight         IV, R           44.4%           34.7%           20.9%	om, 95% C1 1.59, 5.81] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.75, 2.69] witho 95% C1 95% C1 1.50, 6.32] 1.75, 2.69] 1.75, 2.70] 1.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75, 2.75	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarraj, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogenety: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Campbell, 2015 Huo, 2023 Jovin, 2015 Huo, 2023 Jovin, 2015 Muri, 2016 Nogueira, 2018 Sarraj, 2023 Yoshimura, 2022 Total Test for overall effe Test for subgroup d Heterogeneity: Tau <sup>2</sup> Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015 Total Total vorts: Test for overall effect: 2	Events         Total           39         124           39         124           119         233           108         230           67         177           31         100           864         0.00; Chi² = 4. $z = 7.02$ ( $P < C$ $p$ log[OR]           0.8329         1.7918           1.411         1.4563           1.7047         0.6043           0.3853         1.2556           ct: $Z = 8.27$ ( $P$ ifferences: No $z = 0.06$ ; Chi² =         EVT           Events         Total           99         2           94         11           47         1           240         240	Events         T           16         95           95         75           32         13           24, df = 4         900001)           SE         V           0.425         0.5605           0.1591         0.6171           0.3266         0.3266           0.2069         0.3366           0.3522            < 0.00001	otal         Wei           122         10           225         227           2257         228           2257         229           2257         2210           1002         8           887         100           8.887         100           8.887         100           8.4%         5.5%           23.0%         4.6%           12.1%         4.6%           11.0%         10.0%           10.0%         10.0%           10         0%           10         245           146         87           146         87           146         87           146         87           146         87           146         87           146         87           146         87	ght         IV, Random           1.78         3.04 [           1.78         1.89 [           5.5%         1.77 [           5.5%         1.77 [           5.6%         2.67 [           0.04 [         2.77 ]           3.04 [         2.77 ]           3.05 [         2.77 ]           3.06 [         2.17 ]           3.17 [         2.30 [1.0 [           4.00 [2.00 [         4.10 [3.3 [           4.10 [3.3 [         2.30 [           5.50 [2.90 [         1.83 [0.6 ]           3.00 [2.1 [         3.00 [           3.01 [1.2 [         3.00 [           3.02 [2.4 [         1.47 [0.1 ]           3.03 [2.1 [         3.02 [           0.11);   <sup>2</sup> = 35         3.08 [           Weight         IV, R           44.4%         34.7% [           20.9%         100.0% [	m, 95% C1 1.59, 5.61] 1.52, 2.71] 1.21, 2.59] 1.62, 4.32] 1.50, 6.32] 1.50, 6.32] 1.50, 6.32] 1.50, 6.32] 1.75, 2.69] 95% C1 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 00, 5.29] 10, 18.00] 100, 5.60] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.50] 10, 4.53] 17, 4.34] % Odds ratio andom, 95% C 2.01 [1.37, 2.5] 2.70 [1.70, 4.23] 3.74 [1.96, 7, 7] 2.53 [1.83, 3.5]	IV, Random, 95% CI
E	study or Subgroup Bendszus, 2023 Berkhemer, 2015 Huo, 2023 Sarral, 2023 Yoshimura, 2022 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> – Test for overall effect: Study or Subgrou Berkhemer, 2015 Goyal, 2015 Huo, 2023 Jovin, 2015 Murl, 2016 Nogueira, 2018 Sarral, 2023 Yoshimura, 2022 Total Test for overall effec Test for subgroup d Heterogeneity: Tau' Study or Subgroup Berkhemer, 2015 Goyal, 2015 Jovin, 2015 Total Total Total vents: Test for overall effect : Test for overall effect :	Events Total 39 124 39 124 39 124 39 124 119 233 108 230 67 177 31 100 864 364 2, 2, 7, 02 ( $P < C$ p log[OR] 0.8329 1.7918 1.411 1.4563 1.7047 0.6043 1.0986 0.3853 1.2556 ct: Z = 8.27 (P Ifferences: No z = 0.06; Chi <sup>2</sup> = EVT Events Total 99 2 94 1 47 4 240 Z = 5.56 ( $P < 0.0$ )	Events         T           16         95           95         75           32         13           24, df = 4         .000001)           SE         0.425           0.5605         0.5605           0.5605         0.5691           0.6227         0.2069           0.3266         0.3522           < 0.00001	otal         Wei           122         10           225         22           225         100           (P = 0.37           Weight           8.4%           5.23.0%           4.6%           12.1%           12.3.0%           4.6%           12.1%           10.0%           9.3%           11.0%           100.0%           10           e           = 8 (P =           trol           Total           245           146           87           478	ght         IV, Rand           1.78         3.04 [           1.78         1.88 [           1.58         1.77 [           3.08 [         5.5% [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           1.77         3.08 [           0.07         2.17 ]           3.7         6.00 [2.00 ]           4.10 [3.3         6.00 [2.00 ]           4.10 [3.3         3.00 [2.00 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ]           1.83 [0.3]         3.00 [2.01 ] <tr td="">         3.01 [2.01 ]</tr>	m, 95% C1 1.59, 5, 81] 1.59, 5, 81] 1.52, 2, 71] 1.21, 2.59] 1.62, 4, 32] 1.50, 6, 32] 1.75, 2, 69] with 95% C1 95% C1 95% C1 95% C1 95% C1 90, 5, 29] 9, 18, 00] 10, 5, 60] 10, 15, 29] 9, 18, 00] 10, 5, 60] 10, 16, 60] 10, 17, 43] 10, 17, 22, 20] 10, 17, 22, 20] 10, 17, 22, 20] 10, 17, 22, 20] 10, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7, 16, 7	IV, Random, 95% CI

Fig. 2 Efficacy outcomes. A mRS ordinal shift distribution at 90 days. B mRS 0–1. C mRS 0–2. D mRS 0–3. E ENI. F Barthel Index score



Fig. 3 Forest plot of sub-group analysis based on infarct core size showing the odds of functional independence (mRS 0-2)

	EVT + MT		Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.15.1 Large Infarct Core								
Huo, 2023	169	230	67	225	27.6%	2.47 [1.99, 3.06]		
Subtotal (95% CI)		230	-	225	27.6%	2.47 [1.99, 3.06]		
Total events	169		67					
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.23 (P < 0.00001)								
1.15.2 Small Infarct Core								
Albers, 2018	65	83	14	77	12.8%	4.31 (2.65, 7.01)		
Campbell, 2015	33	35	15	35	16.7%	2.20 [1.49, 3.25]		
Noqueira 2018	82	107	39	99	24 0%	1 95 [1 49 2 54]		
Savar 2015	53	6A	21	52	18.9%	2 05 11 45 2 911		
Subtotal (95% CI)		289	-1	263	72.4%	2.37 [1.76, 3.21]	•	
Total events	233		69					
Heterogeneity: $Tau^2 = 0.06$ ; $Ch^2 = 8.26$ , $df = 3$ (P = 0.04); $l^2 = 64\%$								
Test for overall effect: Z = 5.62 (P < 0.00001)								
Total (95% CI)		519		488	100.0%	2.37 [1.92, 2.93]	•	
Total events	402		156					
Heterogeneity: Tau <sup>2</sup> =	0.03; Cł	1 <sup>2</sup> = 8.	75, df =	4 (P =	0.07); 💾	= 54%		
Test for overall effect:	Z = 7.94	I (P < 0	.00001)				U.2 U.3 I 2 3 Eavours (MT) Eavours (EVT+MT)	
Test for subgroup differences: $Chl^2 = 0.04$ , $df = 1$ (P = 0.84), $l^2 = 0\%$								

Fig. 4 Forest plot of sub-group analysis based on infarct core size showing the rates of partial/complete recanalization

### Any intracerebral hemorrhage

Five RCTs enrolling a total of 1305 patients investigated the incidence of any ICH. The pooled analysis showed a statistically significant effect favoring MT alone (OR=1.77, 95% *CI* [1.30–2.42], P=0.007,  $I^2$ =72%) (Fig. 5A). In the sensitivity analysis, removing Khoury et al. [7] yielded statistically significant and homogenous effect ( $OR = 2.06, 95\% CI [1.46-2.92], P < 0.0001, I^2 = 47\%$ ) (Supplementary Fig. 8). Infarct core-based analysis was subsequently performed, with analysis showing that



Fig. 5 Safety outcomes. A Any intracerebral hemorrhage. B Symptomatic intracranial hemorrhage (sICH). C Mortality at 90 days. D Early neurological worsening (ENW)

patients with both large and small infarct cores had insignificant differences between the two groups, although MT alone has lower rates of any ICH (OR=2.93, 95% [1.08–7.95], P=0.03,  $I^2=79\%$ ) and (OR=2.27, 95% [0.86–5.98], P=0.10,  $I^2=37\%$ ), respectively (Supplementary Fig. 9).

### Symptomatic intracranial hemorrhage (sICH)

Fourteen RCTs enrolling 3806 patients assessed the differences in sICH between the two groups. There was no significant difference between the two arms, with a homogeneous effect (OR=1.31, 95% [0.94–1.83], P=0.11,  $I^2=0\%$ ) (Fig. 5B). Infarct core-based analysis was subsequently performed. Analysis of patients with both large and small infarct cores showed insignificant difference between the two groups (OR=1.67, 95% [0.93–3.00], P=0.09,  $I^2=0\%$ ) and (OR=1.04, 95% [0.59–1.84], P=0.90,  $I^2=0\%$ ), respectively (Supplementary Fig. 10).

# Mortality at 90 days

All RCTs assessed the association between mortality at 90 days between the two groups. The pooled estimate revealed that there was no significant difference between the two groups (OR = 0.86, 95% [0.74–1.00], P = 0.05,  $I^2 = 23\%$ ) (Fig. 5C). Visual inspection revealed that the studies were skewed to the right, showing an asymmetrical distribution in the funnel plot (Supplementary Fig. 11). Egger's regression test for funnel plot asymmetry yielded a *t*-statistic of -0.9419 with a *P*-value of 0.3634, indicating no significant evidence of asymmetry. Begg's rank correlation test showed a z-statistic of 0.15 with a P-value of 0.8820, further suggesting no significant evidence of funnel plot asymmetry (Supplementary Fig. 12). Infarct core-based analysis was performed. Large infarct core and small infarct core patients showed insignificant difference between the two groups (OR = 0.85, 95% [0.71– 1.01], P=0.07,  $I^2=0\%$ ) and (OR=0.82, 95% [0.57-1.17]), P = 0.26,  $I^2 = 53\%$ ), respectively (Supplementary Fig. 13).

# Early neurological worsening (ENW)

Five RCTs with 1011 patients assessed ENW. The pooled analysis showed insignificant difference between the two groups (OR = 1.07, 95% *CI* [0.76–1.49], P = 0.71,  $I^2 = 62\%$ ) (Fig. 5D). In a sensitivity analysis, the largest change in heterogeneity occurred when the study by Nogueira et al. [16] was removed, resulting in low heterogeneity (OR = 1.40, 95% *CI* [0.95–2.08], P = 0.09,  $I^2 = 7\%$ ) (Supplementary Fig. 14).

# Parenchymal hematoma

Four RCTs comprising 1297 patients investigated the differences in parenchymal hematoma type 1 between the two arms. There was no statistically significant difference between the two groups, with a homogeneous effect  $(OR=1.03, 95\% [0.55-1.93], P=0.93, I^2=0\%)$  (Supplementary Fig. 15). Seven RCTs comprising 1789 patients assessed the rates of parenchymal hematoma type 2. There was no statistically significant difference between the two groups, with a homogeneous effect  $(OR=1.31, 95\% [0.87-1.97], P=0.20, I^2=0\%)$  (Supplementary Fig. 16).

# Subarachnoid hemorrhage

Four RCTs with a total of 1297 patients assessed the SAH rates of subarachnoid hemorrhage between the two groups. The pooled analysis further demonstrated that MT alone was significantly associated with lower rates of subarachnoid hemorrhage (OR=3.75, 95% [1.44–9.73], P=0.007,  $I^2$ =0%) (Supplementary Fig. 17).

# Discussion

This systematic review and meta-analysis focusing on acute large-vessel ischemic stroke revealed notable improvements in functional outcomes, ENI, Barthel Index score, and partial/complete recanalization when employing EVT in conjunction with medical treatment compared to medical treatment alone. Safety outcome analysis further indicated comparable rates between the two cohorts in terms of mortality, sICH, ENW, and parenchymal hematoma types 1 and 2. Nevertheless, statistically significant differences were observed in the incidences of ICH treatment in terms of the administration of any ICH and subarachnoid treatment. Subgroup analysis based on infarct core size revealed significant improvements in functional independence and recanalization in patients with large or small infarct cores. Moreover, no statistically significant associations were discerned between sICH and mortality at the 90-day mark in either infarct core subgroup.

The homogeneous effects observed in both age groups indicate that EVT consistently improves outcomes in terms of the mRS ordinal shift analysis, regardless of whether the patients are younger or older than 70 years. Clinically, this finding indicates that EVT could be confidently applied across a broad age range, supporting its use as a standard treatment for acute ischemic stroke in both younger and older patients. These results further highlight that age alone should not be a limiting factor when considering EVT, as the benefits extend across different age demographics, potentially including better overall recovery and reduced disability in stroke survivors.

In recent years, endovascular thrombectomy has arisen as the primary standard of care for patients with ischemic stroke with LVO. Many studies have consistently highlighted the advantageous effects of this intervention on functional outcomes and mortality rates. Nonetheless, research regarding the effectiveness and safety of endovascular thrombectomy remains ongoing within specific patient cohorts, such as those with large and small core infarcts, as well as consideration of demographic features [2, 3].

Our meta-analysis focusing on efficacy outcomes, including the reduction of disability scale score at 90 days, excellent functional outcome, functional independence, independent ambulation, ENI, and partial/ complete recanalization, revealed statistically significant improvements, providing robust evidence to support the use of EVT in the management of large-vessel ischemic strokes. Notably, these findings align with previous meta-analyses [2, 20-22]. Consistent outcomes across these analyses underscore the efficacy of endovascular thrombectomy in enhancing functional outcomes after large-vessel ischemic stroke, reinforcing the current imperative for its integration into clinical stroke management practice. Improved functional outcomes, extending beyond the clinical realm, further have a profound impact on the quality of life of stroke survivors. This empowerment enabled them to regain mastery of their daily activities, engage in social interactions, and experience a renewed sense of autonomy. Our meta-analysis establishes a foundational perspective endorsing the efficacy of endovascular thrombectomy in managing both largeand small-infarct core patients, resulting in improved functional outcomes. This observation aligns with earlier meta-analytic findings [23]. The ongoing discourse regarding the efficacy of EVT has been constrained by stringent selection criteria in previous RCTs [24]. Furthermore, our results underscore the efficacy of EVT in improving recanalization across both infarct core groups, although caution is warranted because of the significant heterogeneity. These findings open up avenues for further research, particularly in regards to the appropriateness of EVT for patients with both infarct core types.

Our analysis of safety outcomes revealed no statistically significant differences in terms of sICH, ENW, parenchymal hematoma types 1 and 2, or mortality between the two groups. However, EVT combined with medical treatment was associated with elevated ICH and subarachnoid hemorrhage rates. These findings are consistent with those of Campbell et al. [4], Sarraj et al. [5], Saver et al. [12], and Goyal et al. [2]. The incorporation of EVT in the management of large-vessel ischemic stroke, notwithstanding the associated hemorrhagic risks, was rationalized by the substantial benefits that often outweigh the inherent risks [25]. The results of this subgroup analysis based on infarct core size further support this rationale, particularly among patients with small infarcts, where the benefits of EVT appear to outweigh the risks. However, in patients with large infarcts, the higher incidence of any ICH indicates the need for more in-depth long-term safety trials to fully understand the impact of EVT in this group. This is crucial for optimizing treatment strategies, as well as ensuring the best possible outcomes for all patients. Furthermore, our analysis of patients stratified by infarct core size revealed diminished rates of mortality at the 90-day in both infarct core groups, thus favoring the use of EVT in conjunction with medical treatment. This outcome suggests that EVT may be judiciously applied in a more inclusive manner, extending its consideration to patients with larger infarct cores than those conventionally treated in typical clinical practice.

The heterogeneity observed in the different outcome analyses likely stemmed from key differences in how the studies were designed as well as the patient populations they included. For example, the study by Goyal et al. [11] included patients up to 12 h after stroke onset, compared to the more common 4.5- to 6-h window, likely resulting in better outcomes because these patients may have had stronger collateral circulation and smaller infarcts. The study of Brekhemer et al. [13] further contributed to the variability in recanalization outcomes by including the less common anterior cerebral artery (ACA) occlusions, which behave differently from the more frequently studied MCA and ICA occlusions. Khoury et al. [7] also included patients within 5 h of symptom onset or those with a clinical imaging mismatch, thus possibly including individuals with more severe ischemia and thereby increasing the risk of intracerebral hemorrhage. Finally, Nogueira et al. [19] focused on patients who had either failed IV tPA therapy or were on anticoagulants, groups typically excluded from other studies. These patients likely had more complex strokes, increasing the chances of early neurological worsening. These variations in patient selection, treatment timing, and inclusion criteria explain the observed heterogeneity across the outcomes.

This meta-analysis has several limitations. First, it was conducted using aggregate level data, rather than individual patient data, thus introducing potential constraints on the precision of our findings. Secondly, the presence of heterogeneity among the pooled RCTs presents a substantial challenge in formulating definitive conclusions regarding the efficacy of EVT in a large infarct core population. Potential sources of heterogeneity include variations in patient selection criteria, definition of the infarct core, diverse imaging modalities employed for patient identification, and disparities in the thrombectomy devices and techniques utilized across the studies. Third, the variability in the definitions of sICH may have affected the results despite the  $I^2$  statistic suggesting no substantial heterogeneity. Fourth, the reliance on unmasked neurologists for the estimation of mRS in the study by Bracard et al. [8] further introduced the possibility of bias, potentially influencing the accuracy of functional outcome assessment in the study results. Fifth, potential publication bias was identified, as indicated by the funnel plot asymmetry observed through visual inspection, and further supported by Egger's regression test and Begg's rank correlation test, both of which indicated evidence or borderline evidence of asymmetry. Finally, inadequate reporting of recanalization outcomes in certain studies may have introduced bias, underscoring the importance of interpreting recanalization results with caution and from a multifactorial perspective.

# Conclusion

Overall, our meta-analysis demonstrated that EVT plus medical treatment was associated with significant improvements in functional outcomes, ENI, overall disability reduction at 3 months, and recanalization among patients with large-vessel acute ischemic stroke. Physicians should consider EVT as a standard of care for eligible patients with large vessel occlusion to optimize treatment outcomes and improve overall stroke prognosis and recovery. In addition, EVT plus medical treatment may be considered for patients with a large infarct core. Nevertheless, further studies are warranted to investigate the role of EVT in patients with large infarct cores.

### Abbreviations

EVT	Endovascular thrombectomy								
LVO	Large vessel occlusion								
MM	Medical treatment								
RCTs	Randomized clinical trials								
OR	Odds ratios								
Cls	Confidence intervals								
mRS	Modified Rankin Scale								
AIS	Acute ischemic stroke								
tPA	Intravenous thrombolysis								
PRISMA	Preferred Reporting Items for Systematic Reviews and								
	Meta-Analysis								
ICA	Internal carotid artery								
M1	Middle cerebral artery segment 1								
M2	Middle cerebral artery segment 2								
CENTRAL	Cochrane Central Register of Controlled Trials								
ENI	Early neurological improvement								
ICH	Any intracerebral hemorrhage								
sICH	Symptomatic intracranial hemorrhage								
ENW	Early neurologic worsening								
RoB2	Revised Cochrane risk of bias tool								
RevMan	Review Manager								

# **Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02670-6.

Supplementary Material 1. Table S1: Outcomes Definitions. Table S2: Studies Clinical history. Table S3: Infarct Core Definitions. Fig. S1. Risk of Bias assessment summary. Fig. S2. mRS Ordinal Shift Distribution at 90 Days after Sensitivity analysis. Fig. S3. Sub-group analysis of mRS Ordinal Shift Distribution at 90 Days based on age. Fig. S4. Funnel Plot of Functional Independence (mRS 0–2) at 90 Days. Fig. S5. Egger's Regression Test and Begger's Rank Correlation Test of Functional Independence (mRS 0–2) at 90 Days. Fig. S6. Partial/Complete recanalization. Fig. S7. Partial/Complete recanalization after sensitivity analysis. Fig. S8. Any Intracerebral Hemorrhage after sensitivity analysis. Fig. S9. Forest plot of sub-group analysis based on infarct core size showing the rates of Any Intracerebral Hemorrhage. Fig. S10. Forest plot of sub-group analysis based on infarct core size showing the rates of Symptomatic Intracranial Hemorrhage (sICH). Fig. S11. Funnel Plot of mortality at 90 Days. Fig. S12. Egger's Regression Test and Begger's Rank Correlation Test of Mortality at 90 Days. Fig. S13. Forest plot of sub-group analysis based on infarct core size showing the rates of mortality at 90 days. Fig. S14. Early Neurological Worsening (ENW) after sensitivity analysis. Fig. S15. Parenchymal hematoma type 1. Fig. S16. Parenchymal hematoma type 2. Fig. S17. Subarachnoid Hemorrhage.

### Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

### Authors' contributions

All authors contributed to the conception and design of this study and were engaged in material preparation, data collection, and analysis. The first draft of the manuscript was written by all authors who commented on the previous versions of the manuscript. All the authors have read and approved the final version of the manuscript.

### Funding

No funding was received for the conduct of this study.

### Declarations

**Ethics approval and consent to participate** Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia. <sup>2</sup>King Abdullah International Medical Research Center, Jeddah, Saudi Arabia. <sup>3</sup>Department of Neurosciences, Ministry of the National Guard-Health Affairs, Jeddah, Saudi Arabia. <sup>4</sup>Neuroscience Department, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia.

### Received: 21 April 2024 Accepted: 26 September 2024 Published online: 12 October 2024

### References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics–2015 update: a report from the American Heart Association. Circulation. 2015;131(4):29–322. https://doi.org/10.1161/CIR.000000000 000152.
- Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England). 2016;387(10029):1723–31. https://doi.org/10.1016/S0140-6736(16) 00163-X.
- Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi Al, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. American Heart Association

Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, & Council on Clinical Cardiology. 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. 2013;44(3):870–947.https://doi.org/10.1161/ STR.0b013e318284056a.

- Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. New England J Med. 2015;372(11):1009– 1018. https://doi.org/10.1056/NEJMoa1414792.
- Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, Sundararajan S, Hu YC, Herial NA, Jabbour P, Gibson D, Wallace AN, Arenillas JF, Tsai JP, Budzik RF, Hicks WJ, et al. Trial of endovascular thrombectomy for large ischemic strokes. New England J Med. 2023;388(14):1259–71. https://doi.org/10. 1056/NEJMoa2214403.
- Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(1):38–44. https://doi.org/10.1136/jnnp-2016-314117.
- Khoury NN, Darsaut TE, Ghostine J, Deschaintre Y, Daneault N, Durocher A, Lanthier S, Poppe AY, Odier C, Lebrun LH, Guilbert F, Gentric JC, Batista A, Weill A, Roy D, Bracard S, Raymond J, EASI trial collaborators. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: a randomized care trial. J Neuroradiol. 2017;44(3):198– 202. https://doi.org/10.1016/j.neurad.2017.01.126.
- Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F, THRACE investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15(11):1138–47. https://doi.org/10. 1016/S1474-4422(16)30177-6.
- Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, Grossman A, Altschul D, McDougall C, Blake L, Fitzsimmons BF, Yavagal D, Terry J, Farkas J, Lee SK, Baxter B, et al. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke. 2016;47(9):2331–8. https://doi.org/10.1161/STROK EAHA.116.013372.
- Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. New England J Med. 2015;372(24):2296–306. https://doi.org/10. 1056/NEJMoa1503780.
- Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. New England J Med. 2015;372(11):1019–30. https://doi.org/10.1056/NEJMoa1414905.
- Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. New England J Med. 2015;372(24):2285–95. https://doi.org/10. 1056/NEJMoa1415061.
- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. New England J Med. 2015;372(1):11–20. https://doi.org/10.1056/NEJMoa1411587.
- Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, Matsumaru Y, Matsumoto Y, Kimura K, Takeuchi M, Yazawa Y, Kimura N, Shigeta K, Imamura H, Suzuki I, Enomoto Y, Tokunaga S, Morita K, Sakakibara F, Kinjo N, et al. Endovascular therapy for acute stroke with a large ischemic region. New England J Med. 2022;386(14):1303–13. https://doi.org/10. 1056/NEJMoa2118191.
- 15. Huo X, Ma G, Tong X, Zhang X, Pan Y, Nguyen TN, Yuan G, Han H, Chen W, Wei M, Zhang J, Zhou Z, Yao X, Wang G, Song W, Cai X, Nan G, Li D, Wang

AY, Ling W, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. New England J Med. 2023;388(14):1272–83. https://doi. org/10.1056/NEJMoa2213379.

- Broderick JP, Adeoye O, Elm J. Evolution of the modified Rankin Scale and its use in future stroke trials. Stroke. 2017;48(7):2007–12. https://doi.org/ 10.1161/STROKEAHA.117.017866.
- Bendszus M, Fiehler J, Subtil F, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, openlabel, randomised trial. Lancet. 2023;402(10414):1753–63. https://doi.org/ 10.1016/S0140-6736(23)02032-9.
- Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708–18. https://doi.org/10.1056/NEJMoa1713973.
- Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11–21. https://doi.org/10.1056/NEJMoa1706442.
- Li Q, Abdalkader M, Siegler JE, Yaghi S, Sarraj A, Campbell BCV, Yoo AJ, Zaidat OO, Kaesmacher J, Pujara D, Nogueira RG, Saver JL, Li L, Han Q, Dai Y, Sang H, Yang Q, Nguyen TN, Qiu Z. Mechanical thrombectomy for large ischemic stroke: a systematic review and meta-analysis. Neurology. 2023;101(9):e922–32. https://doi.org/10.1212/WNL.000000000207536.
- Morsi RZ, Elfil M, Ghaith HS, Aladawi M, Elmashad A, Kothari S, Desai H, Prabhakaran S, Al-Mufti F, Kass-Hout T. Endovascular thrombectomy for large ischemic strokes: a living systematic review and meta-analysis of randomized trials. Journal of stroke. 2023;25(2):214–22. https://doi.org/10. 5853/jos.2023.00752.
- Balami JS, Sutherland BA, Edmunds LD, Grunwald IQ, Neuhaus AA, Hadley G, Karbalai H, Metcalf KA, DeLuca GC, Buchan AM. A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. Int J Stroke. 2015;10(8):1168–78. https://doi.org/10.1111/ ijs.12618.
- Zhongxing Y, Zhiqiang L, Jiangjie W, Qing C, Jinfeng Z, Chaoqun W, Feng L. Efficacy and safety of endovascular treatment for acute large-vessel ischemic stroke beyond 6 h after symptom onset: a meta-analysis. Front Neurol. 2021;12: 654816. https://doi.org/10.3389/fneur.2021.654816.
- Zhang J, Yuan C, Deng X, Yuan Q, Wang M, Fu P, Fang J, Du Z, Hu J. Efficacy and safety of endovascular treatment with or without intravenous alteplase in acute anterior circulation large vessel occlusion stroke: a meta-analysis of randomized controlled trials. Neurol Sci. 2022;43(6):3551–63. https://doi.org/10.1007/s10072-022-06017-8.
- Diestro JDB, Dmytriw AA, Broocks G, Chen K, Hirsch JA, Kemmling A, Phan K, Bharatha A. Endovascular thrombectomy for low ASPECTS large vessel occlusion ischemic stroke: a systematic review and meta-analysis. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2020;47(5):612–9. https://doi.org/10.1017/cjn.2020. 71.

# **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.