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Endovascular Treatment vs. Conventional Medical Therapy for Symptomatic Intracranial Atherosclerotic Stenosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Intracranial atherosclerotic stenosis (ICAS) is a leading cause of ischemic stroke, with elevated recurrence risk. The efficacy and safety of endovascular treatment (EVT) versus conventional medical therapy (CMT) remain controversial. **Methods:** We searched PubMed, Embase, Web of Science, and CENTRAL for RCTs comparing EVT + CMT versus CMT alone for sICAS. Primary outcomes: any stroke/death, ischemic stroke, death, ICH, TIA within 30 days. Secondary outcomes: these events beyond 30 days through 1 year and over the entire follow-up. **Results:** Six RCTs (1641 patients) were included. Within 30 days, EVT increased any stroke/death (RR = 2.31; 95% CI: 1.57 - 3.39), ischemic stroke (RR = 1.97; 95% CI: 1.22 - 3.19), ICH (RR = 10.55; 95% CI: 2.90 - 38.38), death (RR = 4.96; 95% CI: 1.28 - 19.21); TIA showed no difference (RR = 0.87; 95% CI: 0.33 - 2.27). From 30 days to 1 year, EVT reduced any stroke/death (RR = 0.10; 95% CI: 0.03 - 0.37); ischemic stroke (RR = 0.49; 95% CI: 0.21 - 1.11) and death (RR = 0.34; 95% CI: 0.08 - 1.40) showed no difference. Over entire follow-up, EVT increased any stroke/death (RR = 1.49; 95% CI: 1.12 - 1.99) and ICH (RR = 5.89; 95% CI: 1.55 - 22.44), reduced ischemic stroke (RR = 0.52; 95% CI: 0.33 - 0.83); death (RR = 1.57; 95% CI: 0.77 - 3.19) and TIA (RR = 0.68; 95% CI: 0.36 - 1.27) showed no difference. **Conclusion:** Current evidence does not support routine EVT for sICAS. EVT may increase 30-day stroke, death, and ICH risks without a clear long-term benefit. Further high-quality RCTs are warranted.

Keywords

Intracranial Atherosclerotic Stenosis, Endovascular Treatment, Conventional Medical Therapy, Stroke

1. Introduction

Intracranial atherosclerotic stenosis (ICAS) is a prominent contributor to ischemic strokes worldwide [1] [2], and is linked to an elevated likelihood of recurrent stroke [3]-[8]. Despite best medical treatment (BMT), individuals with symptomatic ICAS (sICAS) still have a high chance of recurrent stroke [9]. ICAS is prevalent in Asian, African, and Hispanic communities [10]-[12].

From a pathophysiological perspective, sICAS involves two core processes: distal embolism from unstable plaque and hemodynamic impairment leading to hypoperfusion. At the molecular level, vulnerable plaques are characterized by inflammatory activation (macrophages and T lymphocytes secreting TNF-α, IL-6, and MMP-9), enhanced oxidative stress (oxidized LDL promoting foam cell formation), and endothelial dysfunction (reduced nitric oxide bioavailability). These events collectively weaken plaque stability and increase rupture risk. Current approaches to sICAS include conventional medical therapy (CMT), endovascular treatment (EVT), and surgical intervention [13]-[16]. BMT includes dual antiplatelet therapy and rigorous risk factor management, yet the 1-year stroke recurrence risk for severe stenosis (70% - 99%) may still exceed 20% [4]. EVT, primarily percutaneous transluminal angioplasty and stenting (PTAS), has been implemented to improve prognosis. However, its efficacy and safety remain debated.

The SAMMPRIS trial was terminated early due to heightened perioperative risk in the EVT group, showing no superiority over CMT [17]. The VISSIT trial produced analogous findings [18]. Despite unfavorable outcomes, current RCTs have constraints, including stent technology limitations, operator expertise, and patient selection. Ongoing progress includes drug-coated balloons (DCB), drug-eluting stents (DES), and submaximal balloon angioplasty (SBA) [19]-[22].

This updated systematic review and meta-analysis synthesizes existing RCT evidence comparing EVT + CMT versus CMT alone for sICAS, aiming to guide clinical decision-making and set directions for future research.

2. Methods

2.1. Protocol Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in conducting this systematic review and meta-analysis [23]. Given that this study incorporated a comprehensive review and analysis of existing literature, ethical clearance was not necessary. The protocol was registered on PROSPERO with ID: CRD420251181199. The authors confirm that all data supporting the findings of this study are accessible within the article and its supplementary materials.

2.2. Search Strategy

Two independent reviewers (H. Y. G and X. X. S) systematically searched four databases: PubMed (MEDLINE), Embase, Web of Science (WOS), and Cochrane

Central Register of Controlled Trials (CENTRAL) until 20th November 2025. The search strategy utilized a blend of controlled vocabulary, such as Medical Subject Headings (MeSH), along with free-text terms. The primary search terms encompassed "intracranial arterial diseases", "intracranial arteriosclerosis", "intracranial atherosclerotic stenosis", "angioplasty", "stent", and "randomized controlled trial". No restrictions on language or publication status were applied. All search strategies, including the complete ones, are made available in Table S1.

2.3. Eligibility Criteria

The selection criteria for this research adhered to the PICOS framework (population, intervention, comparator, outcome, and study design): (P) Adult patients with ischemic stroke or TIA caused by atherosclerotic stenosis (70% - 99%) of a major intracranial artery (internal carotid artery, the middle cerebral artery, vertebral artery, or basilar artery may be affected. (I) Any form of endovascular intervention (such as balloon angioplasty and/or stent placement) in conjunction with medication therapy; (C) Routine drug therapy. CMT usually comprises antiplatelet medications, statins, and rigorous control of blood pressure, blood sugar levels, and lifestyle factors. (O) Our primary outcomes included any stroke or death, ischemic stroke, death, intracranial hemorrhage (ICH), and transient ischemic attack (TIA) within 30 days. Secondary outcomes encompassed any stroke or death, ischemic stroke, and death occurring between 31 days and 1 year post-randomization. For this landmark analysis, patients who experienced the primary outcome event within the first 30 days were excluded from the denominator for the corresponding secondary outcome because they were no longer at risk. These events, along with ICH and TIA, were also assessed over the entire follow-up period; S, RCTs. The following are exclusion criteria: 1) Non-ICAS, which includes conditions such as aortic dissection, vasculitis, and moyamoya disease. 2) Comprehensive assessments, descriptive analyses, observational investigations, case reports, and commentaries; There were studies that did not have any extractable data available.

2.4. Study Screening and Data Extraction

Two researchers (H. Y. G and X. X. S) independently reviewed the titles and abstracts of the references in the search results to eliminate obviously irrelevant literature. We thoroughly examined the content of the remaining references; the same two researchers (H. Y. G and X. X. S) independently reviewed the studies, identified which to include, and documented the reasons for excluding those that didn't meet the criteria. During the screening process, any disagreements were resolved by discussing or consulting with a third researcher named J. T. Z. For the meta-analysis, exclusively publicly published studies were utilized. ENDNOTE 20 was utilized for managing all references.

Two independent researchers extracted data utilizing a pre-designed stand-

ardized form. The extracted content encompasses fundamental research data such as the name of the first author, the year of publication, the country associated with the study, and the study design employed. The key attributes to consider when studying research subjects include the sample size, age, gender, and medical history. Intervention and control measures: a tailored treatment plan and an appropriate sample size. Outcome data: the number of primary and secondary outcomes, the total number of participants, and the duration of follow-up.

2.5. Risk of Bias

To evaluate the methodological quality of the RCTs that were included, the Cochrane Risk of Bias Assessment Tool was employed [24]. This instrument evaluates the potential for bias across seven distinct areas: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (implementation bias)There are several factors that can introduce bias into research studies, including the blinding of outcome assessors (also known as measurement bias), incomplete outcome data (which is referred to as follow-up bias), selective reporting (a type of reporting bias), and other potential sources of bias. The risk level for each domain was categorized as "low risk" and "high risk". The evaluation process was concluded independently by two researchers, utilizing RevMan 5.4 software for data management and visualization. Two researchers (H. Y. G and X. X. S) independently carried out quality control and bias assessment. All conflicts were addressed through discussion with the corresponding author (J. T. Z).

2.6. Statistical Analysis

The statistical analyses were conducted utilizing RevMan 5.4 software. For binary variables, effect sizes were calculated using the risk ratio (RR) and its 95% confidence interval (CI). In meta-analyses involving zero-event studies, the Mantel-Haenszel method with a continuity correction of 0.5 was applied to both arms of the affected trials to enable calculation of the risk ratio, as implemented in RevMan 5.4. Sensitivity analyses excluding zero-event studies were also considered to assess the robustness of the findings. To evaluate the presence of heterogeneity across studies, both the P-value from the Q test and the I^2 statistic were employed. In the event of substantial variability ($P < 0.05$ or $I^2 > 50\%$), a random-effects model is employed to consolidate the data. Alternatively, when the fixed-effects model is employed [25]. Whenever data permitted, we conducted subgroup analyses to investigate possible sources of heterogeneity. To explore the potential impact of different endovascular techniques, a pre-specified subgroup analysis was planned to compare studies using stent implantation versus those using submaximal balloon angioplasty (SBA) alone. The interaction test (P for interaction) was used to assess whether the treatment effect differed between these subgroups.

2.7. Assessment of the Certainty of Evidence

The certainty of the evidence for each primary and secondary outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [25] [26]. The evidence from randomized controlled trials starts as high certainty but can be downgraded based on five domains: risk of bias (study limitations), inconsistency (unexplained heterogeneity), indirectness (population, intervention, comparator, outcome), imprecision (wide confidence intervals or sparse data), and publication bias. The certainty was categorized into four levels: high, moderate, low, and very low. Two review authors (H. Y. G and X. X. S) independently performed the GRADE assessments. Any disagreements were resolved by discussion or consultation with a third author (J. T. Z). The GRADE evidence profile or "Summary of Findings" table was generated using GRADEpro GDT software (https://gradepro.org).

3. Results

3.1. Study Selection and Screening Process

The initial database search produced 452 records. Following the removal of 43 duplicate entries, the titles and abstracts of 423 distinct records underwent screening. After the title and abstract screening process, a total of 400 records were eliminated. The texts of the remaining 23 articles were obtained and evaluated for eligibility. In the end, six RCTs satisfied the inclusion criteria and were incorporated into both the qualitative synthesis and quantitative meta-analysis. The PRISMA flow diagram (**Figure 1**) provides a summary of the study selection process.

3.2. Characteristics of Included Studies

We incorporated a total of six RCTs [17]-[22]. The main features of the study are outlined in **Table 1**. A total of 1641 individuals with sICAS were included in the study. Of the participants, 817 were allocated to the EVT combined with CMT group, while 824 were assigned to the CMT group. The baseline characteristics are depicted in **Table 2**.

3.3. Risk of Bias

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias tool. As summarized in **Figure 2** and **Figure 3**, all six trials were judged to have a low risk of bias for random sequence generation and allocation concealment. However, due to the nature of the interventions, blinding of participants and personnel was not feasible in any of the included trials, leading to a high risk of performance bias. The risk of detection bias was considered low in most studies as outcome assessors were blinded. Overall, the evidence base is derived from well-conducted RCTs, but the open-label design represents a notable methodological limitation. **Figure 2** and **Figure 3** present an overview of the bias found in the included studies.

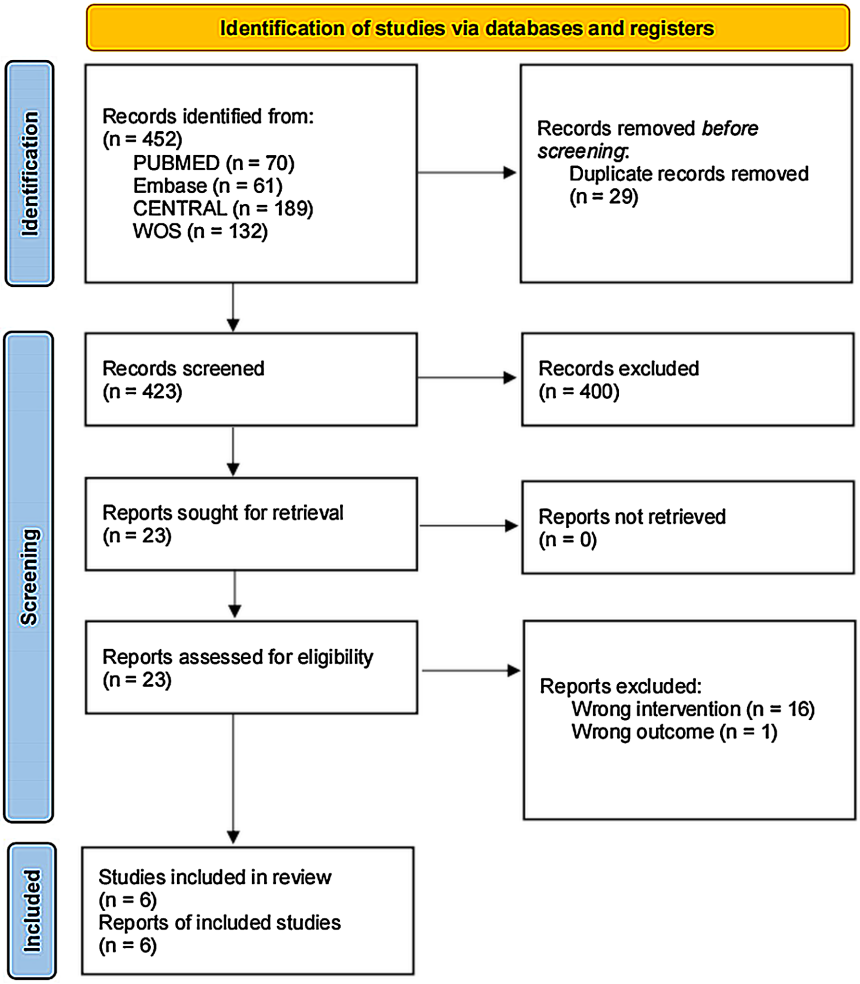


Figure 1. PRISMA flow chart of the screening process.

Table 1. Summary characteristics of the included RCTs [17]-[22].

Author, Year	Recruitment Time	Country	Study Design	Population	Total Population	Intervention Group (n)	Control Group (n)	Follow-Up Period (Months)
Miao *et al.* 2012 [19]	2007-2010	China	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of the middle cerebral artery	70	PTAS + MT (n = 36)	CMT (n = 34)	9.9 ± 3.9 (mean ± SD) for PTAS, 9.7 ± 4.4 (mean ± SD) for control
Derdeyn *et al.* 2014 [17]	2008-2011	USA	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of a major intracranial artery	451	PTAS + MT (n = 224)	CMT (n = 227)	32.4 (median)
Zaidat *et al.* 2015 [18]	2009-2012	International	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of a major intracranial artery	111	PTAS + MT (n = 58)	CMT (n = 53)	12 (median)

Continued

Gao *et al.* 2022 [20]	2014-2016	China	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of a major intracranial artery	358	PTAS + MT (n = 176)	CMT (n = 182)	36 (median)
Sun *et al.* 2024 [21]	2018-2022	China	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of a major intracranial artery, receiving treatment with at least 1 antithrombotic drug and/or risk factor management	501	SBA + MT (n = 249)	CMT (n = 252)	12 (median)
Ip *et al.* 2025 [22]	2006-2021	China	RCT	Patients with recent TIA or stroke caused by 70% - 99% stenosis of a major intracranial artery	150	PTAS + MT (n = 74)	CMT (n = 76)	120 (median)

PTAS: Percutaneous Transluminal Angioplasty and Stenting; SBA: Submaximal Balloon Angioplasty; MT: Medical Therapy; CMT: Conventional Medical Therapy; TIA: Transient Ischemic Attack.

Table 2. Baseline characteristics of the participants.

				History (%)						Qualifying Event (%)	
Author, Year	**Group (n)**	**Ages, Mean ± SD**	**Gender, M**	**HTN**	**HLD**	**DM**	**CAD**	**Smoking, Never/ Former/ Current**	**Alcohol, Never/ Former/ Current**	**TIA**	**Stroke**
Miao *et al.* 2012 [19]	EVT (n = 36)	53.42 ± 13.55	24 (66.7)	23 (63.9)	10 (27.8)	8 (22.2)	3 (9.1)	NR/NR/21 (58.3)	15 (41.7)	29 (81)	7 (19)
	CMT (n = 34)	49.18 ± 9.29	25 (73.5)	15 (44.1)	13 (38.2)	5 (14.7)	5 (14.7)	NR/NR/19 (55.9)	15 (44.1)	26 (76)	8 (24)
Derdeyn *et al.* 2014 [17]	EVT (n = 224)	61.0 ± 10.7	127 (57)	200 (89)	195 (87)	105 (47)	47 (21)	90 (40)/79 (35)/54 (24)	NR	82 (37)	142 (63)
	CMT (n = 227)	59.5 ± 11.8	145 (64)	203 (89)	202 (89)	103 (45)	59 (26)	78 (34)/80 (35)/69 (30)	NR	75 (33)	152 (67)
Zaidat *et al.* 2015 [18]	EVT (n = 58)	61.8 ± 12.28	41 (70.7)	49 (84.5)	29 (50.0)	25 (43.1)	10 (17.2)	25 (43.1)/22 (37.9)/11 (19.0)	NR	24 (41.4)	36 (62.1)
	CMT (n = 53)	61.8 ± 12.82	32 (60.4)	43 (81.1)	32 (60.4)	20 (37.7)	12 (22.6)	24 (45.3)/17 (32.1)/12 (22.6)	NR	22 (41.5)	34 (64.2)
Gao *et al.* 2022 [20]	EVT (n = 176)	56.7 ± 9.4	128 (72.7)	117 (66.5)	18 (10.2)	57 (32.4)	19 (10.8)	96/39 (22.2)/41 (23.3)	NR/25 (14.2)/30 (17.0)	87 (49.4)	89 (50.6)
	CMT (n = 182)	55.9 ± 9.8	135 (74.2)	125 (68.7)	21 (11.5)	44 (24.2)	19 (10.4)	94/38 (20.9)/50 (27.5)	NR/22 (12.1)/32 (17.6)	77 (42.3)	105 (57.7)

Continued

Sun *et al.* 2024 [21]	EVT (n = 249)	58.3 ± 9.7	172 (69.1)	181 (72.7)	176 (70.7)	82 (32.9)	NR	NR/NR/60 (24.1)	NR	34 (13.7)	215 (86.4)
	CMT (n = 252)	58.3 ± 9.7	171 (67.9)	185 (73.4)	191 (75.8)	87 (34.5)	NR	NR/NR/66 (26.2)	NR	44 (17.5)	208 (82.5)
Ip *et al.* 2025 [22]	EVT (n = 74)	62 ± 10	51 (69)	51 (69)	54 (73)	30 (41)	NR	NR/NR/30 (41)	NR/NR/19 (26)	22 (30)	52 (70)
	CMT (n = 76)	61 ± 9.0	54 (71)	53 (70)	54 (71)	26 (34)	NR	NR/NR/36 (47)	NR/NR/19 (25)	22 (30)	58 (76)

EVT: Endovascular Treatment; CMT: Conventional Medical Therapy; HTN: Hypertension; HLD: Hyperlipidemia; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; TIA: Transient Ischemic Attack; NR: Not Report.

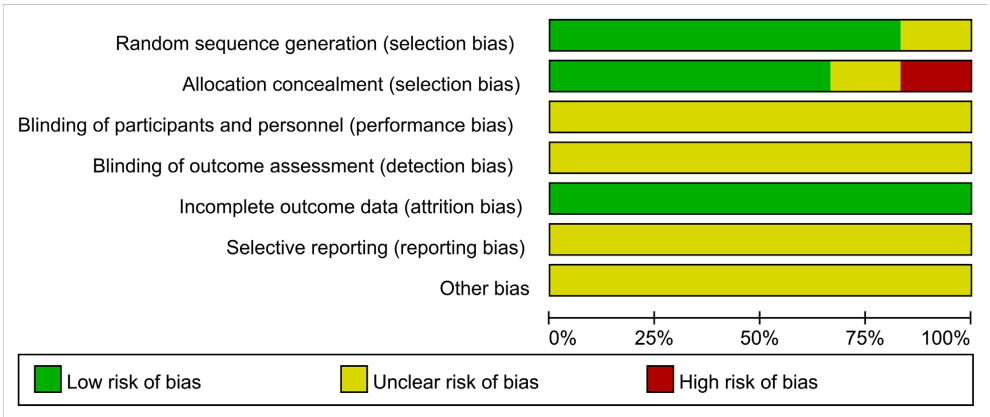


Figure 2. Risk of bias graph.

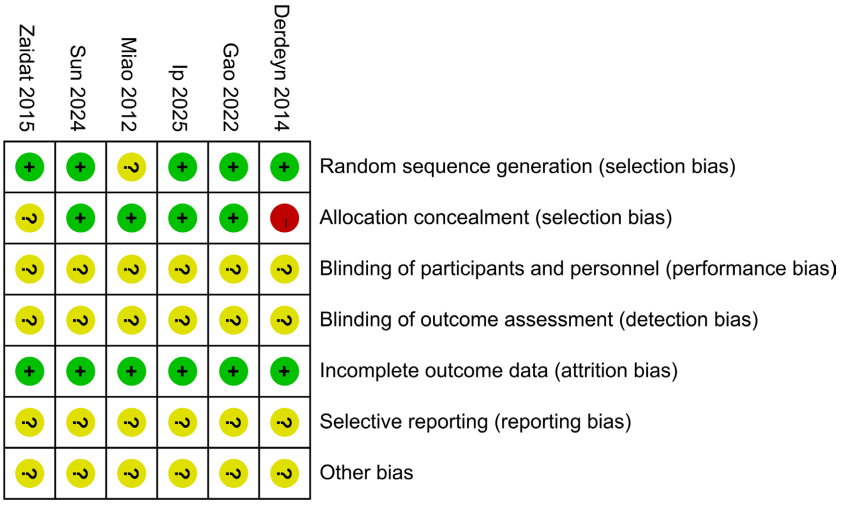


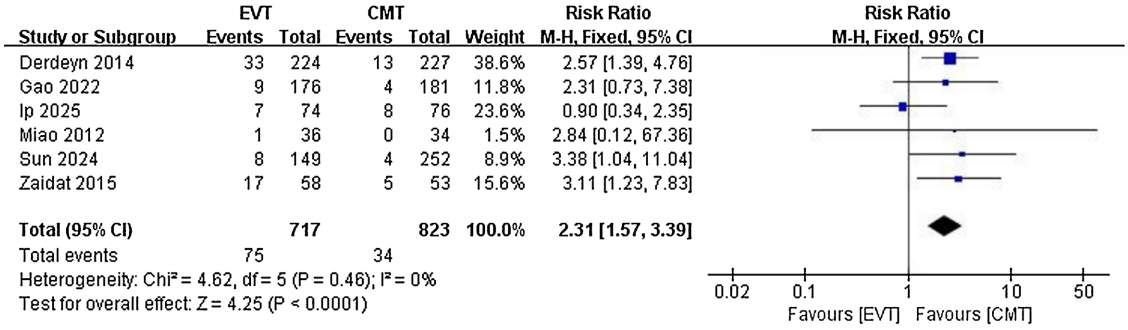
Figure 3. Risk of bias summary.

3.4. Meta-Analysis Results

3.4.1. Primary Outcome

Within 30 days: six studies reported the outcome of any stroke or death (**Figure 4(a)**), with outcome data available for 1540 of the 1641 randomized patients

a



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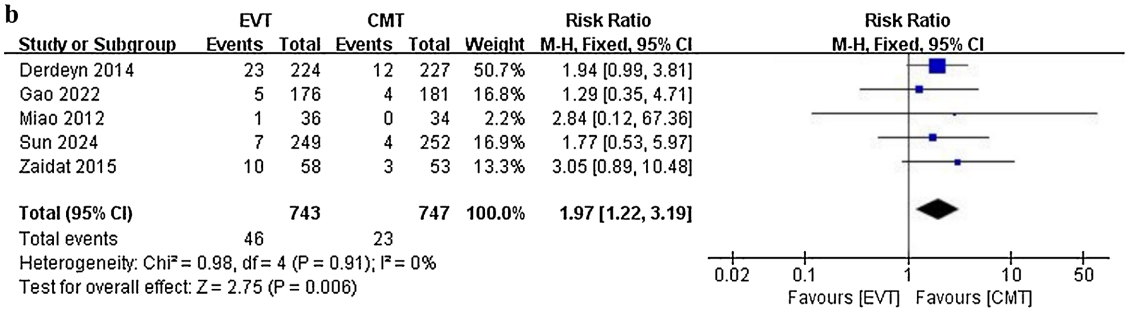

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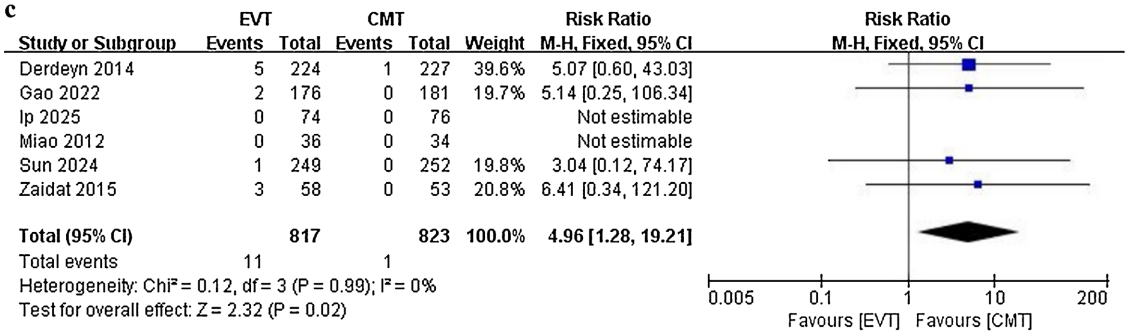

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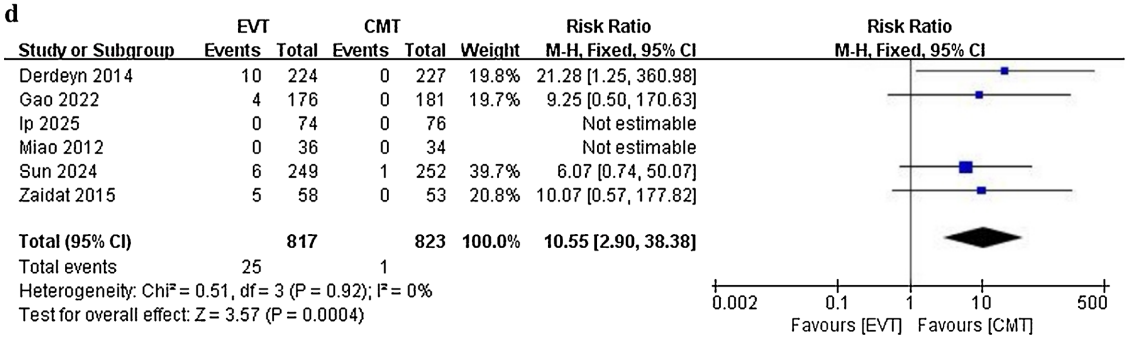

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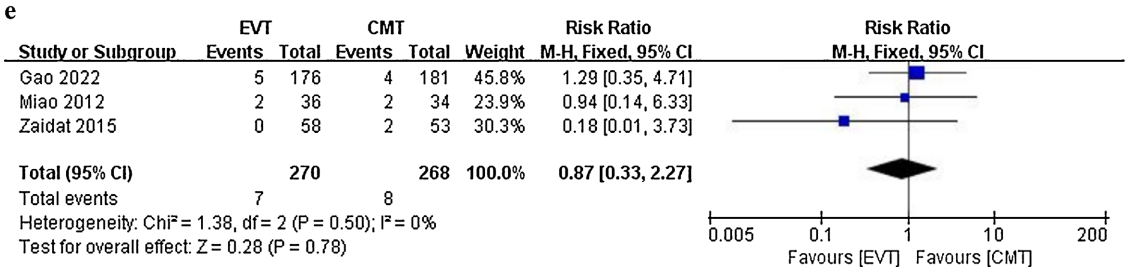

Figure 4. Primary endpoints within 30 days.

(EVT: 717; CMT: 823). The risk of any stroke or death was significantly higher in the EVT group than in the CMT group (RR = 2.31; 95% CI: 1.57 - 3.39; P < 0.0001), with no heterogeneity observed among studies (P = 0.46; I^2 = 0%). Five studies reported any ischemic stroke (Figure 4(b)), with outcome data available for 1490 of the 1641 randomized patients. EVT significantly increased the risk of ischemic stroke (RR = 1.97; 95% CI: 1.22 - 3.19; P = 0.006), with no heterogeneity among studies (P = 0.91; I^2 = 0%). Six studies reported all-cause death (Figure 4(c)), with outcome data available for 1640 of the 1641 randomized patients. The risk of death was significantly higher in the EVT group than in the CMT group (RR = 4.96; 95% CI: 1.28 - 19.21; P = 0.02), with no heterogeneity among studies (P = 0.99; I^2 = 0%). Six studies reported ICH (Figure 4(d)), with outcome data available for 1640 of the 1641 randomized patients. The risk of ICH was significantly higher in the EVT group than in the CMT group (RR = 10.55; 95% CI: 2.90 - 38.38; P = 0.0004), with no heterogeneity among studies (P = 0.92; I^2 = 0%). Three studies reported TIA (Figure 4(e)), with a sample size of 538. No significant difference was observed between the two groups (RR = 0.87; 95% CI: 0.33 - 2.27; P = 0.78), and there was no heterogeneity among studies (P = 0.50; I^2 = 0%). The summary of these results is presented in Table 3.

In an exploratory subgroup analysis stratified by endovascular device type, the increased risk of any stroke or death within 30 days appeared to be consistent across trials using stenting (RR = 2.57; 95% CI: 1.68 - 3.93) and the single trial

Table 3. Overview of primary and secondary outcomes in patients with symptomatic intracranial stenosis treated with EVT vs. CMT.

Outcome	Studies (n)	RR (95% CI)	P-Value for Cochran Q	I^2 (%)	P-Value
Any stroke or death within 30 days	6	2.31, 95% CI: 1.57 - 3.39	0.46	0	<0.0001
Any ischemic stroke within 30 days	5	1.97, 95% CI: 1.22 - 3.19	0.91	0	0.006
Death within 30 days	6	4.96, 95% CI: 1.28 - 19.21	0.99	0	0.02
ICH within 30 days	6	10.55, 95% CI: 2.90 - 38.38	0.92	0	0.0004
TIA within 30 days	3	0.87, 95% CI: 0.33 - 2.27	0.50	0	0.78
Any stroke or death beyond 30 days through 1 year	3	0.10, 95% CI: 0.03 - 0.37	0.47	0	0.0006
Any ischemic stroke beyond 30 days through 1 year	5	0.49, 95% CI: 0.21 - 1.11	0.08	52	0.09
Death beyond 30 days through 1 year	5	0.34, 95% CI: 0.08 - 1.40	1.00	0	0.13
Any stroke or death during the entire follow-up	5	1.49, 95% CI: 1.12 - 1.99	0.14	45	0.007
Any ischemic stroke during the entire follow-up	5	0.52, 95% CI: 0.33 - 0.83	0.24	30	0.006
Death in the entire follow-up	5	1.57, 95% CI: 0.77 - 3.19	0.61	0	0.22
ICH in the entire follow-up	4	5.89, 95% CI: 1.55 - 22.44	0.68	0	0.009
TIA in the entire follow-up	4	0.68, 95% CI: 0.36 - 1.27	0.14	46	0.22

RR: Risk Ratio; CI: Confidence Interval; EVT: Endovascular Treatment; CMT: Conventional Medical Therapy; ICH: Intracranial Hemorrhage; TIA: Transient Ischemic Attack.

using SBA (RR = 1.55; 95% CI: 0.62 - 3.88), with no significant interaction between subgroups (P for interaction = 0.31). These findings should be interpreted with caution, given the limited number of studies in each subgroup.

3.4.2. Secondary Outcomes

Beyond 30 days through 1 year: Three studies reported any stroke or death between 31 days and 1 year (**Figure S1(a)**), with a total of 571 patients who were event-free at 30 days included in this landmark analysis. The risk of CMT outcome was higher in the CMT group than in the EVT group (RR = 0.10, 95% CI: 0.03 - 0.37; P = 0.0006), with no heterogeneity among studies (P = 0.47; I^2 = 0%). Five studies reported any ischemic stroke (**Figure S1(b)**), with a sample size of 1529. There was no statistically significant difference in this outcome between the two groups (RR = 0.49, 95% CI: 0.21 - 1.11; P = 0.09), with moderate heterogeneity among studies (P = 0.08; I^2 = 52%). We conducted a subgroup analysis to explore the impact of stent type on the outcome (**Figure S3**). Five studies reported deaths (**Figure S1(c)**), with a sample size of 1490. There was no significant difference in the incidence of the outcome event between the two groups (RR = 0.34, 95% CI: 0.08 - 1.40; P = 0.13). There was no heterogeneity among the studies (P = 1.00; I^2 = 0%).

In the entire follow-up, five studies reported any stroke or death outcome throughout the follow-up endpoint (**Figure S2(a)**), with a sample size of 970. EVT was significantly associated with an increased risk of any stroke or death (RR = 1.49; 95% CI: 1.12 - 1.99; P = 0.007), with low heterogeneity among studies (P = 0.14; I^2 = 45%). Five studies reported any ischemic stroke (**Figure S2(b)**), with a sample size of 839. The risk of CMT was higher in the CMT group than in the EVT group (RR = 0.52; 95% CI: 0.33 - 0.83; P = 0.006), with low heterogeneity among studies (P = 0.24; I^2 = 30%). Five studies reported deaths (**Figure S2(c)**), with a sample size of 1452. The results were not significantly different (RR = 1.57; 95% CI: 0.77 - 3.19; P = 0.22), and there was no heterogeneity among the studies (P = 0.61; I^2 = 0%). Four studies reported ICH (**Figure S2(d)**), with a sample size of 1379. The ICH risk in the EVT group was significantly higher than that in the CMT group (RR = 5.89; 95% CI: 1.55 - 22.44; P = 0.009), with no heterogeneity among studies (P = 0.68; I^2 = 0%). Four studies reported TIA (**Figure S2(e)**), with a sample size of 836. The results showed no significant difference (RR = 0.68; 95% CI: 0.36 - 1.27; P = 0.22), with low heterogeneity among studies (P = 0.14; I^2 = 46%).

3.5. Certainty of Evidence

The GRADE assessment demonstrates that EVT is significantly associated with a substantial increase in the risks of death within 30 days, stroke recurrence, ischemic stroke, and intracranial hemorrhage. The certainty of evidence for the 30-day outcomes is mostly high. In contrast, the certainty of evidence for secondary outcomes is generally moderate, and there remains a certain degree of uncertainty regarding the risks of any stroke or death. Although certain outcomes suggest potential trends of benefit or harm, the imprecision and inconsistency of specific results necessitate a cautious interpretation of the long-term effects (**Table 4**).

Table 4. GRADE summary of findings table: certainty of evidence for primary and secondary outcomes.

Certainty Assessment						Study Event Rates (%)		Relative Effect (95% CI)	Risk Difference	Certainty
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	With [EVT]	With [CMT]			
Any stroke or death within 30 days										
1540 (6 RCTs)	not serious	not serious	not serious	not serious	none	75/717 (10.5%)	34/823 (4.1%)	RR 2.31 (1.57 to 3.39)	54 more per 1000 (from 24 more to 99 more)	⊕⊕⊕⊕ High
Any ischemic stroke within 30 days										
1490 (5 RCTs)	not serious	not serious	not serious	not serious	none	46/743 (6.2%)	23/747 (3.1%)	RR 1.97 (1.22 to 3.19)	30 more per 1000 (from 7 more to 67 more)	⊕⊕⊕⊕ High
Death within 30 days										
1640 (6 RCTs)	not serious	not serious	not serious	serious[b]	none	11/817 (1.3%)	1/823 (0.1%)	RR 4.96 (1.28 to 19.21)	5 more per 1000 (from 0 fewer to 22 more)	⊕⊕⊕◯ Moderate[b]
ICH within 30 days										
1640 (6 RCTs)	not serious	not serious	not serious	serious[b]	none	25/817 (3.1%)	1/823 (0.1%)	RR 10.55 (2.90 to 38.38)	12 more per 1000 (from 2 more to 45 more)	⊕⊕⊕◯ Moderate[b]
TIA within 30 days										
538 (3 RCTs)	not serious	serious[a]	not serious	serious[b]	none	7/270 (2.6%)	8/268 (3.0%)	RR 0.87 (0.33 to 2.27)	4 fewer per 1000 (from 20 fewer to 38 more)	⊕⊕◯◯ Low
Any stroke or death beyond 30 days through 1 year										
571 (2 RCTs)	not serious	serious[a]	not serious	not serious	none	2/285 (0.7%)	24/286 (8.4%)	RR 0.10 (0.03 to 0.37)	76 fewer per 1000 (from 81 fewer to 53 fewer)	⊕⊕⊕◯ Moderate[b]
Any ischemic stroke beyond 30 days through 1 year										
1529 (5 RCTs)	not serious	serious[c]	not serious	not serious	none	24/759 (3.2%)	51/770 (6.6%)	RR 0.49 (0.21 to 1.11)	34 fewer per 1000 (from 52 fewer to 7 more)	⊕⊕⊕◯ Moderate[a]
Death beyond 30 days through 1 year										
1490 (5 RCTs)	not serious	not serious	not serious	not serious	none	2/743 (0.3%)	7/747 (0.9%)	RR 0.34 (0.08 to 1.40)	6 fewer per 1000 (from 9 fewer to 4 more)	⊕⊕⊕⊕ High
Any stroke or death during the entire follow-up										
970 (4 RCTs)	not serious	not serious	not serious	serious[b]	none	96/486 (19.8%)	64/484 (13.2%)	RR 1.49 (1.12 to 1.99)	65 more per 1000 (from 16 more to 131 more)	⊕⊕⊕◯ Moderate[b]

Continued

Any ischemic stroke during the entire follow-up										
839 (3 RCTs)	not serious	not serious	not serious	serious[b]	none	26/427 (6.1%)	48/412 (11.7%)	RR 0.52 (0.33 to 0.83)	56 fewer per 1000 (from 78 fewer to 20 fewer)	⊕⊕⊕◯ Moderate[b]
Death in the entire follow-up										
1452 (5 RCTs)	not serious	not serious	not serious	serious[b]	none	19/727 (2.6%)	12/725 (1.7%)	RR 1.57 (0.77 to 3.19)	9 more per 1000 (from 4 fewer to 36 more)	⊕⊕⊕◯ Moderate[b]
ICH in the entire follow-up										
1379 (4 RCTs)	not serious	not serious	not serious	not serious	none	14/685 (2.0%)	2/694 (0.3%)	RR 5.89 (1.55 to 22.44)	14 more per 1000 (from 2 more to 62 more)	⊕⊕⊕⊕ High
TIA in the entire follow-up										
836 (4 RCTs)	not serious	not serious	not serious	serious[b]	none	16/426 (3.8%)	22/410 (5.4%)	RR 0.68 (0.36 to 1.27)	17 fewer per 1000 (from 34 fewer to 14 more)	⊕⊕⊕◯ Moderate[b]

CI: Confidence Interval; RR: Risk ratio; RCTs: Randomized Controlled Trials; EVT: Endovascular Treatment; CMT: Conventional Medical Therapy; ICH: Intracranial Hemorrhage; TIA: Transient Ischemic Attack. Explanations: [a]Low number of events (<300 events); [b]A wide confidence interval that does not exclude the appreciable harm/benefit (downgraded for imprecision); [c]$I^2 > 50\%$.

4. Discussion

This meta-analysis confirms that EVT is strongly linked to increased short-term adverse events, especially during the 30-day perioperative period. The heightened risks of ICH and mortality are particularly significant. This phenomenon can be explained at both anatomical and molecular levels. Anatomically, intracranial arteries lack an external elastic lamina, have a thin media, and are characterized by a tortuous course and abundant perforators (e.g., lenticulostriate arteries), making them vulnerable to mechanical injury. At the molecular level, mechanical stretch triggers an "inflammation-thrombosis cascade": damaged endothelium releases vWF and P-selectin, recruiting platelets; mechanical injury activates the NLRP3 inflammasome, cleaving pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, amplifying local inflammation. In patients with pre-existing hypoperfusion, sudden reperfusion can trigger ischemia-reperfusion injury, characterized by a ROS burst, calcium overload, and MMP-9-mediated disruption of the blood-brain barrier, thereby explaining the >10-fold increased ICH risk with EVT (RR = 10.55). Perforator occlusion involves the "snowplowing effect" and local tissue factor release [27].

Although the 30-day to 1-year analysis showed a lower risk of any stroke or death in the EVT group, this finding requires cautious interpretation and does not negate the overall conclusion that EVT offers no substantial long-term benefit. The sustained benefit of CMT has a solid molecular basis. Dual antiplatelet therapy targets COX-1 and $P2Y_{12}$, synergistically inhibiting platelet aggregation. Statins

exert pleiotropic effects: inhibiting NF-κB to reduce TNF-α, IL-6, and MMP-9; promoting collagen synthesis to stabilize plaques; upregulating eNOS to improve endothelial function; and reducing tissue factor and PAI-1. These molecular actions enable CMT to stabilize vulnerable plaques at their source, an effect unachievable by angioplasty alone. Our findings align with SAMMPRIS, VISSIT, and recent meta-analyses [28]-[31]. Thus, comprehensive CMT—including dual antiplatelet therapy, statins, and risk factor control—remains the primary treatment for most sICAS patients.

However, CMT has limitations. Some patients on BMT continue to experience recurrent stroke. The molecular mechanisms of CMT failure include: Antiplatelet drug resistance—~30% of patients have loss-of-function CYP2C19 alleles causing inadequate clopidogrel activation; Residual inflammatory risk—persistently elevated hs-CRP (>2 mg/L) despite LDL control, indicating sustained IL-6/TNF-α production driving plaque instability; Hemodynamic maladaptation—chronic hypoperfusion induces HIF-1α stabilization, upregulating VEGF and pro-apoptotic molecules, leading to pathological angiogenesis and neuronal metabolic crisis not reversible by CMT. This study has limitations: the small number of RCTs limits statistical power; the considerable technical heterogeneity among EVT procedures, including device type (stents vs. balloons) and procedural timing, may have influenced the pooled results. The limited number of RCTs precluded a robust subgroup analysis to evaluate the efficacy of different techniques, which represents an important limitation of our study. Moderate heterogeneity in some secondary outcomes suggests uncontrolled confounders [15] [16].

Future studies should integrate mechanism-based imaging and molecular biomarkers for precise patient selection. At the imaging level, high-resolution MRI assesses plaque vulnerability (intraplaque hemorrhage, enhancement), while perfusion imaging (CTP/ASL) and CFD evaluate hemodynamic impairment. At the molecular level, CYP2C19 genotyping can guide antiplatelet adjustment (e.g., switching to ticagrelor), and hs-CRP/IL-6 measurement can identify candidates for anti-inflammatory therapy (e.g., low-dose colchicine). Novel EVT devices (DCB, DES) release antiproliferative agents that inhibit neointimal hyperplasia, but their impact on endothelial healing requires evaluation. Future RCTs should incorporate molecular stratification to identify subgroups likely to benefit from EVT (e.g., patients with hemodynamic failure without extensive perforator disease) [4] [32] [33]. Additionally, postponing EVT for several weeks after symptom onset and centralizing procedures in high-volume centers may lower perioperative risks [19] [20].

5. Conclusion

Drawing upon the latest evidence, this meta-analysis reveals that in sICAS, EVT poses higher perioperative risks and offers no long-term advantage over CMT. These risks are mechanistically linked to intracranial arterial fragility and molecular events (NLRP3 activation, MMP-9-mediated BBB disruption). CMT failure

involves CYP2C19 resistance and residual inflammation (elevated hs-CRP). Hence, comprehensive CMT should remain the primary standard of care. Future studies should integrate molecular biomarkers with advanced imaging to identify patients who may benefit from revascularization, while evaluating safer techniques in biomarker-stratified trials.

Availability of Data and Materials

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

Authorship Contribution

Hanying Gu: Writing—original draft, writing—review & editing, software, project administration, methodology, formal analysis, data curation, and conceptualization. **Xiuxia Shi:** Writing—original draft, writing—review & editing, supervision, project administration, data curation, and conceptualization. **Jiangtao Zhang:** Writing—original draft, writing—review & editing, supervision, project administration, methodology, funding acquisition, formal analysis, data curation, and conceptualization.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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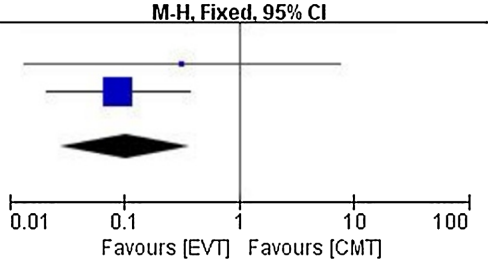
Supplementary Information

a

Study or Subgroup	EVT Events	EVT Total	CMT Events	CMT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Derdeyn 2014	11	224	16	227		Not estimable
Miao 2012	0	36	1	34	6.3%	0.32 [0.01, 7.48]
Sun 2024	2	249	23	252	93.7%	0.09 [0.02, 0.37]
Total (95% CI)		**285**		**286**	**100.0%**	**0.10 [0.03, 0.37]**
Total events	2		24			

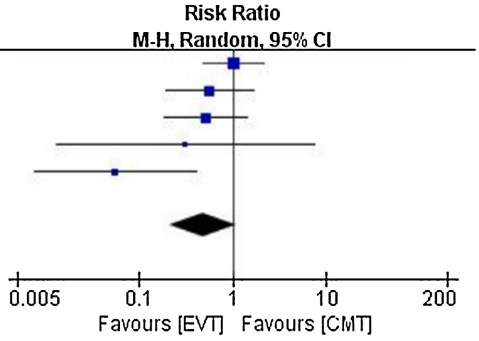
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.45 (P = 0.0006)



b

Study or Subgroup	EVT Events	EVT Total	CMT Events	CMT Total	Weight	Risk Ratio M-H, Random, 95% CI
Derdeyn 2014	13	224	13	227	31.5%	1.01 [0.48, 2.14]
Gao 2022	5	176	9	181	24.7%	0.57 [0.20, 1.67]
Ip 2025	5	74	10	76	25.7%	0.51 [0.18, 1.43]
Miao 2012	0	36	1	34	5.9%	0.32 [0.01, 7.48]
Sun 2024	1	249	18	252	12.1%	0.06 [0.01, 0.42]
Total (95% CI)		**759**		**770**	**100.0%**	**0.49 [0.21, 1.11]**
Total events	24		51			

Heterogeneity: Tau² = 0.42; Chi² = 8.37, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 1.71 (P = 0.09)



c

Study or Subgroup	EVT Events	EVT Total	CMT Events	CMT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Derdeyn 2014	2	224	6	227	80.0%	0.34 [0.07, 1.66]
Gao 2022	0	176	0	181		Not estimable
Miao 2012	0	36	0	34		Not estimable
Sun 2024	0	249	1	252	20.0%	0.34 [0.01, 8.24]
Zaidat 2015	0	58	0	53		Not estimable
Total (95% CI)		**743**		**747**	**100.0%**	**0.34 [0.08, 1.40]**
Total events	2		7			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.13)

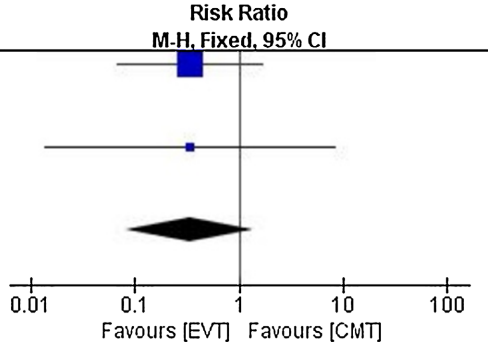


Figure S1. Secondary outcomes beyond 30 days through 1 year.

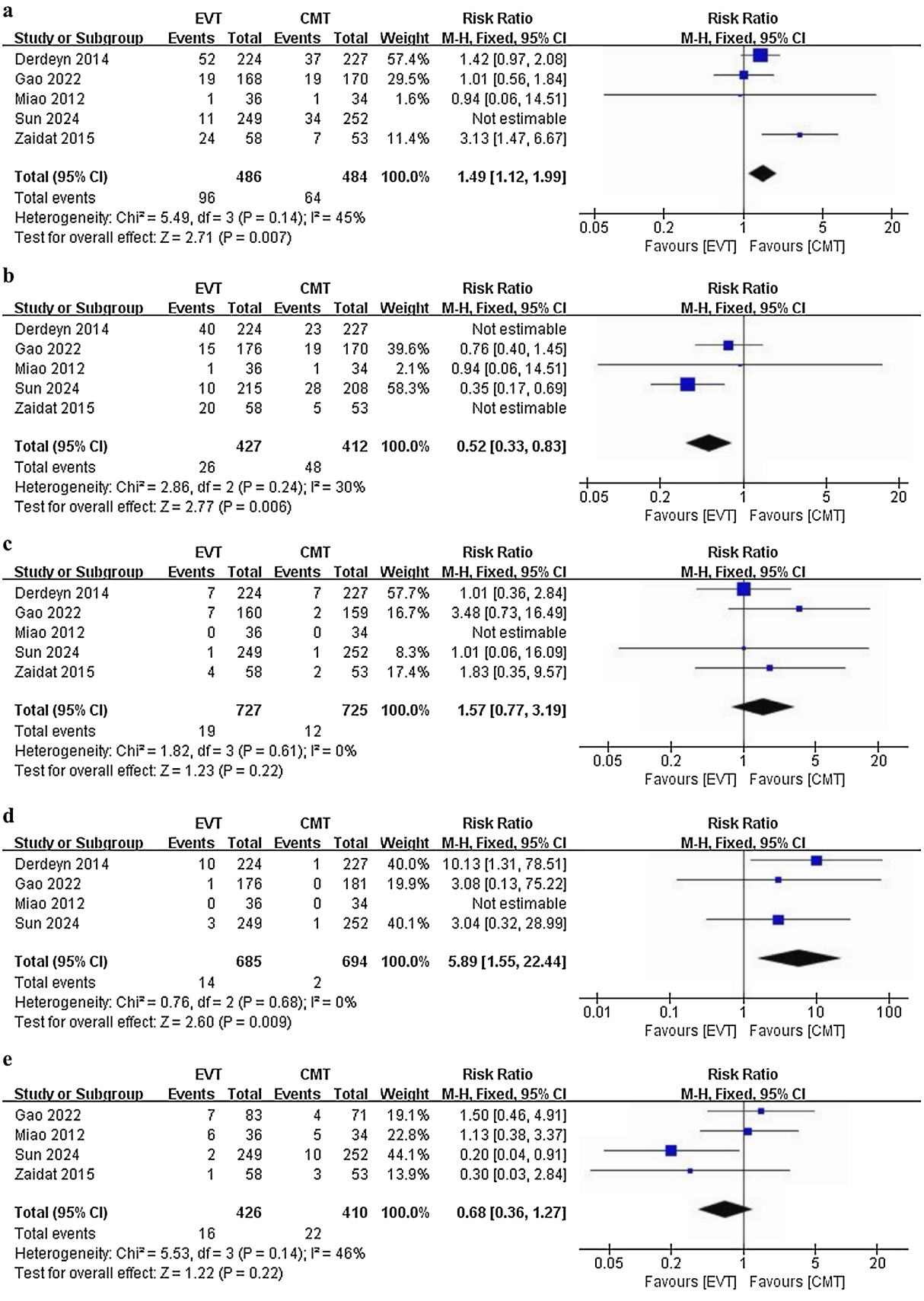


Figure S2. Secondary outcomes in the entire follow-up.

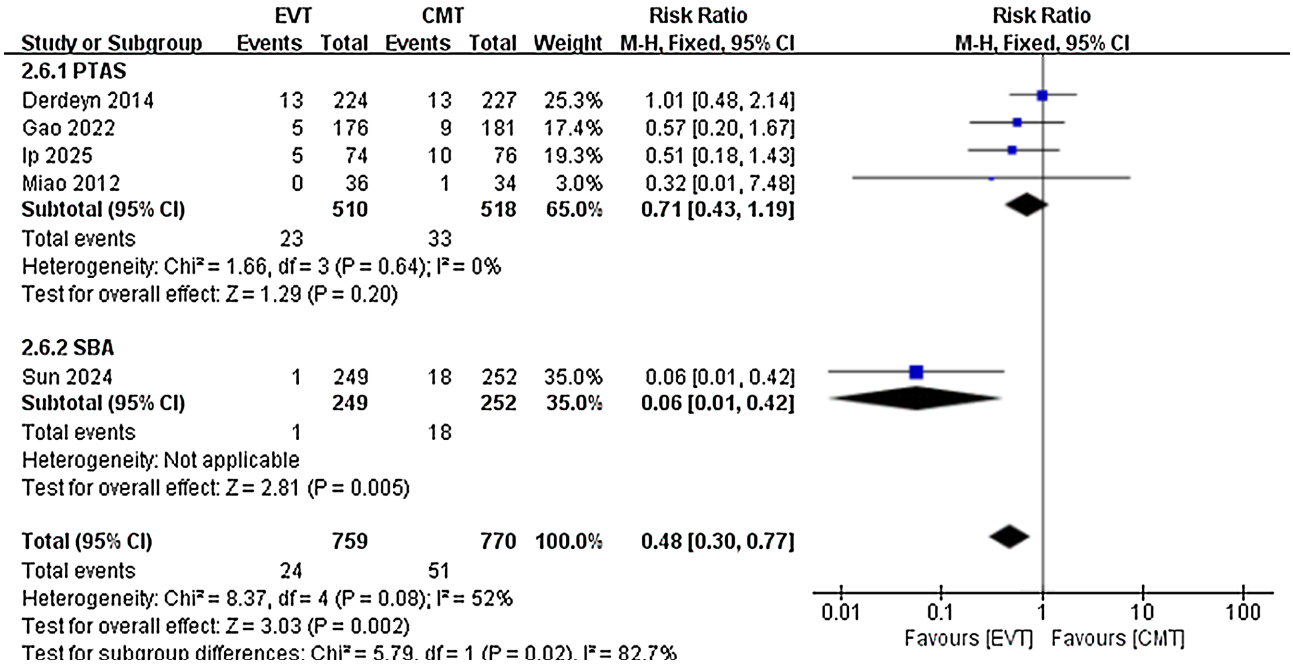


Figure S3. Forest plot comparing the risk of any ischemic stroke beyond 30 days through 1 year, after stratification according to stenting device.

Table S1. Search strategy.

Datebase	Search Terms	Results
PUBMED	#1 "Intracranial Arteriosclerosis"[Mesh] #2 ((((((((((((Arteriosclerоses, Intracranial[Title/Abstract]) OR (Arteriosclerosis, Intracranial[Title/Abstract])) OR (Intracranial Arteriosclerоses[Title/Abstract])) OR (Cerebral Arteriosclerosis[Title/Abstract])) OR (Arteriosclerоses, Cerebral[Title/Abstract])) OR (Arteriosclerosis, Cerebral[Title/Abstract])) OR (Cerebral Arteriosclerоses[Title/Abstract])) OR (Cerebral Atherosclerosis[Title/Abstract])) OR (Atherosclerоses, Cerebral[Title/Abstract])) OR (Atherosclerosis, Cerebral[Title/Abstract])) OR (Cerebral Atherosclerоses[Title/Abstract])) OR (Intracranial Atherosclerosis[Title/Abstract])) OR (Atherosclerоses, Intracranial[Title/Abstract])) OR (Atherosclerosis, Intracranial[Title/Abstract])) OR (Intracranial Atherosclerоses[Title/Abstract]) #3 #1 OR #2 #4 "Intracranial Arterial Diseases"[Mesh] #5 ((((((((((((((((Arterial Disease, Intracranial[Title/Abstract]) OR (Intracranial Arterial Disease[Title/Abstract])) OR (Arterial Diseases, Intracranial[Title/Abstract])) OR (Intracranial Arterial Disorders[Title/Abstract])) OR (Arterial Disorder, Intracranial[Title/Abstract])) OR (Arterial Disorders, Intracranial[Title/Abstract])) OR (Intracranial Arterial Disorder[Title/Abstract])) OR (Brain Diseases, Arterial[Title/Abstract])) OR (Arterial Brain Disease[Title/Abstract])) OR (Arterial Brain Diseases[Title/Abstract])) OR (Arterial Diseases, Brain[Title/Abstract])) OR (Arterial Disease, Brain[Title/Abstract])) OR (Arterial Disease, Brain[Title/Abstract])) OR (Brain Arterial Diseases[Title/Abstract])) OR (Brain Disorders, Arterial[Title/Abstract])) OR (Arterial Brain Disorder[Title/Abstract])) OR (Arterial Brain Disorders[Title/Abstract])) OR (Brain Disorder, Arterial[Title/Abstract]) #6 #4 OR #5 #7 #3 OR #6 #8 "Angioplasty"[Mesh]	70

	#9 (((((((((Angioplasties[Title/Abstract]) OR (Endoluminal Repair[Title/Abstract])) OR (Endoluminal Repairs[Title/Abstract])) OR (Repair, Endoluminal[Title/Abstract])) OR (Repairs, Endoluminal[Title/Abstract])) OR (Angioplasty, Transluminal[Title/Abstract])) OR (Transluminal Angioplasty[Title/Abstract])) OR (Percutaneous Transluminal Angioplasty[Title/Abstract])) OR (Angioplasty, Percutaneous Transluminal[Title/Abstract])) OR (Transluminal Angioplasty, Percutaneous[Title/Abstract]) #10 #8 OR #9 #11 "Stents"[Mesh] #12 Stent[Title/Abstract] #13 #11 OR #12 #14 #10 OR #13 #15 "Randomized Controlled Trials as Topic"[Mesh] #16 ((Clinical Trials, Randomized[Title/Abstract]) OR (Trials, Randomized Clinical[Title/Abstract])) OR (Controlled Clinical Trials, Randomized[Title/Abstract]) #17 #15 OR #16 #18 #7 AND #14 AND #17	
Embase	#1 'intracranial arterial stenosis'/exp #2 'intracranial arterial narrowing':ti,ab,kw OR 'intracranial arterial narrowings':ti,ab,kw OR 'intracranial arterial stenoses':ti,ab,kw OR 'intracranial arteries stenoses':ti,ab,kw OR 'intracranial arteries stenosis':ti,ab,kw OR 'intracranial artery narrowing':ti,ab,kw OR 'intracranial artery stenoses':ti,ab,kw OR 'intracranial artery stenosis':ti,ab,kw OR 'narrowing of the intracranial arteries':ti,ab,kw OR 'stenoses of the intracranial arteries':ti,ab,kw OR 'stenosis of the intracranial arteries':ti,ab,kw OR 'stenosis of the intracranial artery':ti,ab,kw OR 'intracranial arterial stenosis':ti,ab,kw #3 #1 OR #2 #4 'angioplasty'/exp #5 'stent'/exp #6 'stent'/exp #7 #5 OR #6 #8 #4 OR #7 #9 'randomized controlled trial (topic)'/exp #10 ('pragmatic clinical trials as topic':ti,ab,kw OR 'randomized controlled trials':ti,ab,kw OR 'randomized controlled trials as topic':ti,ab,kw OR 'randomized controlled trial':ti,ab,kw) AND topic:ti,ab,kw #11 #9 OR #10 #12 #3 AND #8 AND #11	61
WOS	#1 intracranial artery stenosis (Topic) #2 Angioplasty OR Angioplasties OR Endoluminal Repair OR Endoluminal Repairs OR Repair, Endoluminal OR Repairs, Endoluminal OR Angioplasty, Transluminal OR Transluminal Angioplasty OR Percutaneous Transluminal Angioplasty OR Angioplasty, Percutaneous Transluminal OR Transluminal Angioplasty, Percutaneous (Topic) #3 stent OR stents (Topic) #4 #2 OR #3 #5 randomized controlled trial OR clinical trials, randomized OR trials, randomized clinical OR controlled clinical trials, randomized (Topic) #3 #1 AND #4 AND #5	132
Cochrane	#1 MeSH descriptor: [Intracranial Arterial Diseases] explode all trees #2 (Intracranial Arterial Disorder):ti,ab,kw #3 (Arterial Disease, Intracranial: ti,ab,kw OR Intracranial Arterial Disease: ti,ab,kw OR Intracranial Arterial Disorders: ti,ab,kw OR Arterial Disorders, Intracranial: ti,ab,kw OR Arterial Disorder,	192

	Intracranial: ti,ab,kw OR Arterial Diseases, Intracranial: ti,ab,kw OR Arterial Brain Disorder: ti,ab,kw OR Brain Disorder, Arterial: ti,ab,kw OR Brain Arterial Diseases: ti,ab,kw OR Arterial Brain Disease: ti,ab,kw OR Brain Disorders, Arterial: ti,ab,kw OR Brain Arterial Disease: ti,ab,kw OR Arterial Brain Disorders: ti,ab,kw OR Arterial Diseases, Brain: ti,ab,kw OR Brain Diseases, Arterial: ti,ab,kw OR Arterial Disease, Brain: ti,ab,kw OR Arterial Brain Diseases):ti,ab,kw
	#4 #1 OR #2 OR #3
	#5 MeSH descriptor: [Angioplasty] explode all trees
	#6 (Angioplasty, Transluminal:ti,ab,kw OR Transluminal Angioplasty:ti,ab,kw OR Percutaneous Transluminal Angioplasty:ti,ab,kw OR Angioplasty, Percutaneous Transluminal:ti,ab,kw OR Transluminal Angioplasty, Percutaneous:ti,ab,kw OR Repair, Endoluminal:ti,ab,kw OR Repairs, Endoluminal:ti,ab,kw OR Endoluminal Repair:ti,ab,kw OR Endoluminal Repairs:ti,ab,kw OR Angioplasties):ti,ab,kw
	#7 #5 OR #6
	#8 MeSH descriptor: [Stents] explode all trees
	#9 (stent):ti,ab,kw
	#10 #8 OR #9
	#11 #7 OR #10
	#12 #4 AND #11

ICAS: Intracranial Arterial Diseases; EVT: Endovascular Therapy; CMT: Conventional Medical Treatment; RCT: Randomized Controlled Trials.

Table S2. Abbreviations.

ICAS	Intracranial Atherosclerosis Stenosis
sICAS	Symptomatic Intracranial Atherosclerosis Stenosis
CMT	Conventional Medical Therapy
EVT	Endovascular Treatment
BMT	Best Medical Treatment
PTAS	Percutaneous Transluminal Angioplasty and Stenting
RCTs	Randomized-Controlled Clinical Trials
DCB	Drug-Coated Balloon
BMS	Bare-Metal Stent
DES	Drug-Eluting Stents
SBA	Submaximal Balloon Angioplasty
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
ICH	Intracranial Hemorrhage
TIA	Transient Ischemic Attack
RevMan	Review Manager
RR	Risk Ratio
CI	Confidence Interval
HR-MRI	High-Resolution Magnetic Resonance Imaging
CTP	Computed Tomography Perfusion
ASL	Arterial Spin Labeling
CFD	Computational Fluid Dynamics