Stroke

ORIGINAL CONTRIBUTION

Risk of Early Recurrent Stroke and Thrombotic Events After Reperfusion Therapy in Acute Ischemic Stroke: A Meta-Analysis

Rezan Ashayeri Ahmadabad, MD; Kaitlyn Sobchuk, MSc; Sunpreet Kaur Cheema, MA; P.N. Sylaja, DM; Mohammed Almekhalfi, MD; Aviraj Deshmukh, MD; Jesse Dawson, MD PhD; Sung-Il Sohn, MD, PhD; Laura C. Gioia, MD, MSc; Ashfaq Shuaib, MD; Brian H. Buck, MD, MSc; Mahesh Kate, MD, MSc

BACKGROUND: Following an acute ischemic stroke, the risk of recurrent stroke is highest in the first 90 days. It is unclear whether this risk is altered by reperfusion therapy. In this meta-analysis, we aim to evaluate the risk of early recurrent stroke and other nonstroke thrombotic events postreperfusion therapy in acute ischemic stroke.

METHODS: In this meta-analysis, randomized controlled trials (RCTs) were included in adults aged 18 years or older with acute ischemic stroke, comparing reperfusion treatment with best medical management (MED). We searched PUBMED, Embase, Cochrane Library, and Web of Science databases. The studies were grouped into endovascular thrombectomy (EVT) versus MED and intravenous thrombolysis versus MED. We performed a meta-analysis using a random-effects model (restricted maximum likelihood) to estimate the log risk ratio of early recurrent stroke and nonstroke thrombotic events (NSTE)—including myocardial infarction, acute coronary syndrome, deep vein thrombosis, pulmonary embolism, and peripheral embolism—after reperfusion therapy compared with MED at 90 days after symptom onset. This study is registered with PROSPERO (The International Prospective Register of Systematic Reviews).

RESULTS: A total of 15 RCTs (n=4898) comparing EVT versus MED observed no difference in early recurrent stroke (5.5%, 143/2618 versus 4.5%, 102/2280; RR, 1.2 [95% CI, 0.9–1.6]). Nine RCTs (n=7193) comparing intravenous thrombolysis versus MED observed no difference in early recurrent stroke (2%, 73/3615 versus 1.8%, 66/3578; RR, 1.1 [95% CI, 0.8–1.5]). Fourteen RCTs (n=4033) comparing EVT versus MED reported NSTE. There was no difference in NSTE in the EVT arm (3.1%, 62/2024 versus 3.1%, 62/2009; RR, 1 [95% CI, 0.7–1.4]). Five RCTs (n=4961) comparing intravenous thrombolysis versus MED observed no difference in NSTE (2%, 51/2479 versus 2.2%, 54/2482; RR, 0.9 [95% CI, 0.6–1.4]).

CONCLUSIONS: Reperfusion therapies (EVT±intravenous thrombolysis) in acute ischemic stroke within 24 hours of symptom onset were not associated with increased recurrent stroke or NSTE within 90 days compared with best medical therapy.

REGISTRATION: URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42024542020.

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

Key Words: acute coronary syndrome ■ atherosclerosis ■ myocardial infarction ■ pulmonary embolism ■ thrombectomy

Patients with acute ischemic stroke (AIS) have an elevated risk of recurrent stroke and other thrombotic events in the first 90 days.[1] The rate of stroke recurrence is 3.4% to 5.3% in the first 90 days after the index stroke.[2,3] This risk is particularly elevated in patients with large artery atherosclerosis and

Correspondence to: Mahesh Kate, MD, MSc, Division of Neurology, Department of Medicine, Faculty of Medicine and Dentistry, Member, Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada. Email mahesh@ualberta.ca
This manuscript was sent to Irene L. Katzan, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.125.050672.
For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
BASIS	Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis
ESCAPE NA1	Safety and Efficacy of Nerinetide [NA-1] in subjects Undergoing Endovascular Thrombectomy for Stroke
EVT	endovascular thrombectomy
IVT	intravenous thrombolysis
MED	best medical management
NSTE	nonstroke thrombotic events
PROSPERO	The International Prospective Register of Systematic Reviews
RCT	randomized controlled trial

cardioembolic stroke etiologies.[4] In addition, patients with ischemic stroke have an increased likelihood of developing venous thromboembolism and acute myocardial infarction (MI). The chance of venous thromboembolism is 20× greater in the first month after AIS, and 11× greater between 1 and 3 months.[5] Myocardial injury is seen in 11% to 26% of patients during the acute phase, whereas the probability of MI within 90 days remains lower at 0.3%.[6]

To prevent early recurrent stroke, guidelines vary depending on whether patients received reperfusion therapies (ie, intravenous thrombolysis [IVT] and endovascular thrombectomy [EVT]).[7,8] In patients with noncardioembolic stroke not receiving these therapies, those with minor deficits are typically treated with short-duration dual antiplatelet therapy. In contrast, following reperfusion with IVT and EVT, patients are usually treated with a single antiplatelet agent regardless of infarct size or deficit severity. This approach persists despite evidence suggesting that patients who undergo EVT may be at higher risk for early recurrent stroke due to factors like reocclusion, distal embolism, or systemic issues like hypercoagulability and cardiac stress.[9,10] Early recurrence mechanisms are multifactorial; large-vessel occlusions may result from incomplete reperfusion or reocclusion, whereas cardiac embolism may occur due to arrhythmias or cardiomyopathy exacerbated by stroke.[11] Given that stroke recurrence and thrombotic events in the subacute phase are influenced by factors such as stroke cause, reperfusion success, use of antiplatelet/anticoagulant therapies, and risk factor control,[8,12,13] it is critical to understand whether reperfusion therapy alters these risks.

In this meta-analysis, we aim to evaluate the risk of early recurrent stroke and nonstroke thrombotic events postreperfusion therapy in AIS.

METHODS

This study has been registered with PROSPERO (The International Prospective Register of Systematic Reviews). Institutional review board approval and informed consent were not required for this meta-analysis. Data supporting the results of this study can be obtained from the corresponding author on reasonable request. This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[14]

Search Strategy

We conducted a comprehensive literature search in PubMed, Embase, and the Cochrane Library from database inception until August 2024. Search terms included "acute ischemic stroke," "reperfusion therapy," "endovascular thrombectomy," "intravenous thrombolysis," and "non-stroke thrombotic events". ("clinical trial" [Publication Type] AND "stroke" [MeSH Terms] OR "stroke" [All Fields] OR "strokes" [All Fields] OR "strokes" [All Fields]) AND ("endovascular" [All Fields] AND "thrombectomy" [MeSH Terms] OR "thrombectomy" [All Fields] OR "thrombectomies" [All Fields]) AND (randomized controlled trial [Filter]). ("clinical trial" [Publication Type] AND "stroke" [MeSH Terms] OR "stroke" [All Fields] OR "strokes" [All Fields] OR "strokes" [All Fields]) AND ("intravenous" [All Fields] OR "intravenously" [All Fields] OR "intravenous" [All Fields] OR "intravenously" [All Fields] AND "Thrombolysis" [All Fields] AND randomizedcontrolledtrial [Filter]). We applied the following filters to the database software to allow studies with: human studies, clinical trials, randomized clinical trials, both male and female subjects, adult subjects, English and non-English language articles, and abstract or full-text availability.

Eligibility Criteria

We included randomized controlled trials (RCTs) involving adult patients (≥18 years) with AIS, comparing reperfusion therapy (EVT and IVT) with standard of care±Placebo with full text available in the English language. Studies reporting early recurrent stroke (within 90 days) and nonstroke thrombotic events (NSTE), including acute coronary syndrome, ST elevation MI, non-ST elevation MI, pulmonary thromboembolism, and deep venous thrombosis, were included. Leg swelling, respiratory distress, stable angina, cardiac complications, neurological worsening, or transient ischemic attack were not considered outcome events. Exclusion criteria were (1) studies with nonrandomized design, nonhuman subjects, or lacking outcome measures, outcome data, and (2) protocols, multiple publications, review articles, case reports, conference abstracts, and guidelines.

In this study, symptomatic embolization in new territories was classified as a recurrent stroke if it resulted in new, clinically significant neurological deficits and was associated with corresponding imaging findings. Although embolization in new territories is conventionally considered a procedural complication, we categorized symptomatic embolization in new territories as recurrent stroke to reflect its clinical impact on patient outcomes.

Data Extraction

Three independent reviewers (R.A.A., K.S., and S.K.C.) extracted relevant data, including study characteristics (author name, publication year, sample size), patient demographics (age, sex, baseline characteristics), treatment modalities (types

of reperfusion therapy and best medical therapy), and outcome measures related to early recurrent stroke and NSTE. Recurrent stroke was defined as any report of recurrent stroke or recurrent ischemic stroke. Cerebral infarction in a new territory without symptoms and intracerebral hemorrhage without further clarification if it occurred in a new territory were excluded. For most studies, the outcome events were reported in the Supplemental Material table describing the adverse events or serious adverse events. Reviewer discrepancies were resolved through discussion and consensus with the fourth reviewer (M.K.). We excluded patients with missing data for the variables and outcomes of interest from our analysis (Figure 1).

Risk of Bias Assessment

To evaluate the risk of bias across the included studies, we used the Cochrane Risk of Bias Tool, focusing on key domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias.[9] Each domain was assessed as having a low, high, or unclear risk of bias. Two reviewers (R.A.A. and S.K.C.) independently assessed the risk of bias. Any disagreements were resolved by consensus, with input from a third senior reviewer (M.K.) when needed.

Statistical Analysis

Meta-analysis was conducted to assess the occurrence of early recurrent stroke and NSTE in the EVT group and IVT alone groups compared with the best medical management (MED) individually. The reason for individual analysis was the baseline differences in the study groups; EVT studies were more likely to have patients with severe neurological deficits. We used a random-effects model (restricted maximum likelihood) to estimate the log risk ratio (log RR) for early recurrent stroke and

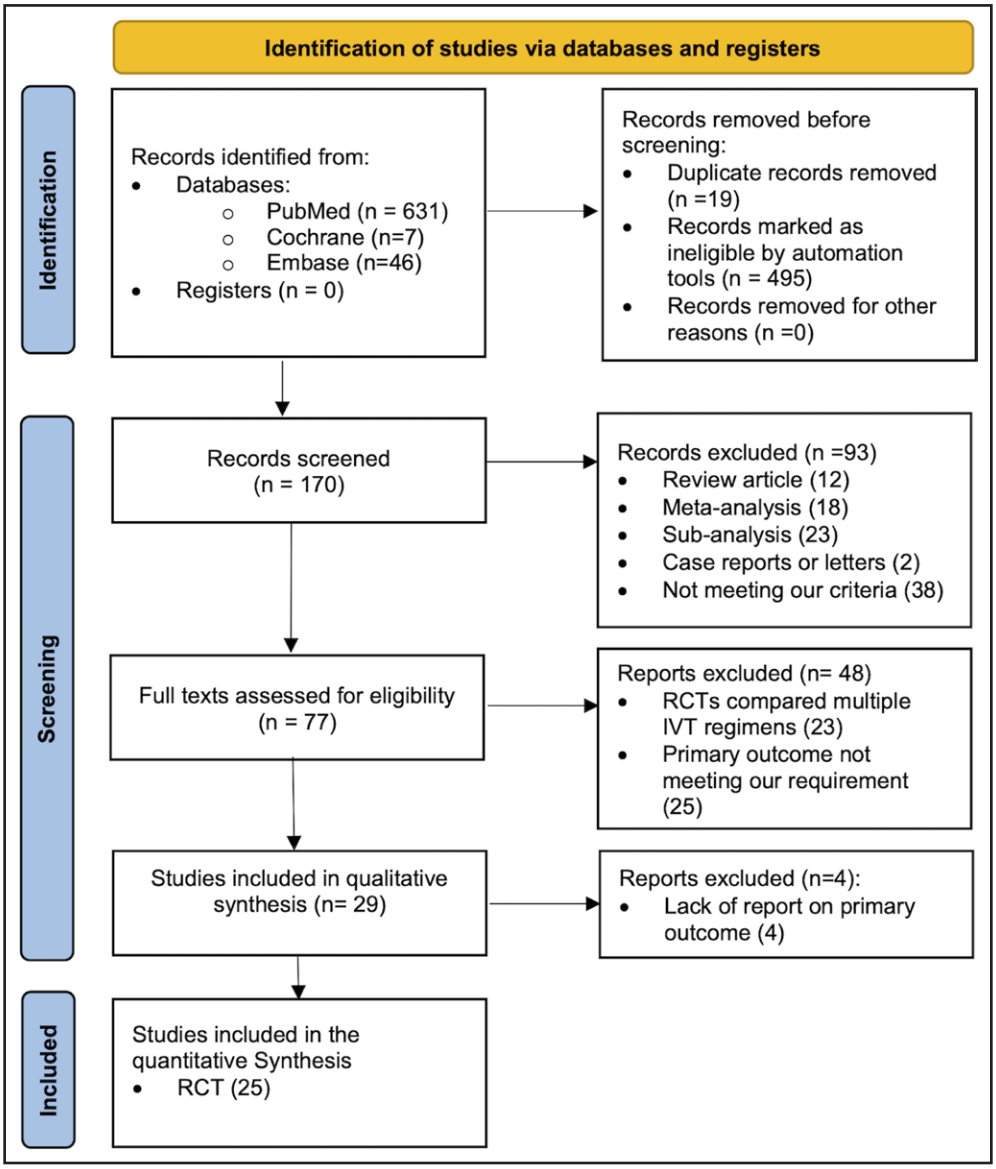

Figure 1. Flowchart of literature review and selection.
Inbuilt filters (automation tools) in the database were applied (human studies, clinical trials, randomized clinical trials, adult [male and female] subjects, English and non-English language articles). IVT indicates intravenous thrombolysis; and RCT, randomized controlled trial.

Table 1. Characteristics of Included Studies Endovascular Thrombectomy Group

Author, y	Study population	N	Intervention	Control	Primary outcomes (intervention vs control arm)
Bendszus et al0[15]	Age ≥18 y, AIS, symptom onset ≤21 h, and ASPECTS 3–5	253	EVT+standard care	Standard care	RS: 30 (23.4%, n=128) vs 35 (28%, n=125)
					RIS is less than RS: 17 (13.3%, n=128) vs 20 (16%, n=125)
					ACS/MI: 0 (0%, n=128) vs 2 (1.6%, n=125)
					Peripheral artery thrombosis/ischemia: 1 (0.8%, n=128) vs 1 (0.8%, n=125)
Berkhemer et al[16]	Age ≥18 y, AIS, symptom onset ≤6 h, and NIHSS score ≥2	500	EVT or IAT or both+standard care	Standard care	RS: 13 (5.6%, n=233) vs 1 (0.4%, n=267)
					Cardiac ischemia: 1 (0.4%, n=233) vs 4 (1.5%, n=267)
Bracard et al[17]	Age 18–80 y, AIS, and NIHSS score 10–25	412	IVT+EVT	IVT	RS: Not reported
					Embolization in new territories: 9 (6%, n=204) vs 0 (0%, n=208)
					PE: 1 (0.5%, n=208) in medical arm
Broderick et al[18]	Age 18–82 y, AIS, symptom onset ≤3 h, and NIHSS score ≥10, 8–9 if intracranial occlusion	656	EVT (Merci retriever, penumbra system, solitaire)+IV tPA	IV tPA alone	RS: 22 (5.1%, n=434) vs 14 (6.3%, n=222)
					NSTE: not reported
Costalat et al[19]	Age 18–80 y, AIS, and NIHSS score ≥6	362	IA tPA±EVT	IV tPA alone	RS: 4 (2.2%, n=181) vs 4 (2.2%, n=181)
					ACS: 4 (2.2%, n=181) vs 2 (1.1%, n=181)
					DVT/PE: 2 (1.1%, n=181) vs 0 (0%, n=181)
Costalat et al[19]	Age ≥18 y, AIS, symptom onset ≤6.5 h, NIHSS score ≥6, baseline mRS score 0–1, and ASPECTS ≤5	324	EVT	Standard care	RS: 11 (6.9%, n=159) vs 2 (1.2%, n=165)
					DVT: 1 (0.6%, n=159) vs 0 (0%, n=165)
					PE: 2 (1.3%, n=159) vs 7 (4.2%, n=165)
					MI: 2 (1.3%, n=159) vs 0 (0%, n=165)
Goyal et al[20]	Age ≥18 y, AIS, symptom onset ≤12 h, ASPECTS 6–10, and moderate to good collateral circulation	315	EVT+standard care	Standard care	RS: 8 (4.8%, n=165) vs 3 (2%, n=150)
					ACS: 2 (1.2%, n=165) vs 1 (0.6%, n=150
					DVT/PE: 2 (1.2%, n=165) vs 2 (1.3%, n=150)
Jovin et al[21]	Age 18–80 y, AIS, 6–24 h from symptom onset, NIHSS score ≥6, and occlusion of BA, or the intracranial part of both VAs	217	EVT	Standard care	RS: not reported
					ACS: 0 (0%, n=110) vs 4 (4%, n=107)
					DVT/PE: 1 (0.9%, n=110) vs 3 (2.8%, n=107)
Jovin et al[22]	Age 18–80 y, AIS, symptom onset ≤8 h, and NIHSS score ≥6	206	EVT (solitaire stent retriever)+standard care	Standard care	RS: 4 (3.9%, n=103) vs 3 (2.9%, n=103)
					Embolization in new territories: 5 (4.9%, n=103) vs 0 (0%, n=103)
					ACS: 1 (1%, n=103) vs 1 (1%, n=103)
					DVT/PE: 3 (2.9%, n=103) vs 6 (5.8%, n=103)
Kidwell et al[23]	Age 18–85, AIS, baseline mRS score 0–2, NIHSS score: 6–29, and TICA, M1, or M2 occlusion	118	EVT (Merci retriever or Penumbra system)	Standard care	They have not split the groups. RS: 7 (5.9%, n=118, both groups together)
					Embolization in new territories: 1 (1.6%, n=64, in the intervention group)
					DVT: 2 (1.7%, n=118, both groups together)
Langezaal et al[24]	Age 18-85 y old,* AIS, symptom onset <6 h, NIHSS score ≥10,* and BA occlusion	300	EVT±IAT	Standard care	RS: 13 (8.4%, n=154) vs 10 (6.8%, n=146)

(*Continued*)

Table 1. Continued

Author, y	Study population	N	Intervention	Control	Primary outcomes (intervention vs control arm)
					ACS: 3 (1.9%, n=154) vs 2 (1.4%, n=146)
Martins et al[25]	Age ≥18 y, AIS, NIHSS score ≥8, baseline mRS 0–1, ASPECTS 6–10, and TICA or M1 occlusion and ischemic core <70 mL on perfusion imaging	221	EVT (Medtronic and Penumbra thrombectomy, no intracranial stent)+standard care	Standard care	RS: 0 (0%, n=111) vs 2 (1.8%, n=110)
					Embolization in new territories: 4 (3.6%, n=111) vs 0 (0%, n=110)
					ACS: 2 (2%, n=111) vs 2 (2%, n=110)
					PE: 3 (2.7%, n=111) vs 0 (0%, n=111)
Muir et al[26]	Age ≥18 y, AIS, intracranial ICA, M1, or M2 single occlusion	65	IVT+EVT with any operator-selected CE-marked device	IVT alone	RS: 3 (9.1%, n=33) vs 0 (0%, n=32)
					MI/ACS: 2 (6.1%, n=33) vs 1 (3.1%, N=32)
Nogueira et al[27]	Age ≥18 y, AIS, symptom onset 6–24 h, NIHSS score ≥10, baseline mRS 0–1, TICA, or M1 occlusion, and no IAT	206	EVT (FDA-approved Trevo Retriever)+standard care	Standard care alone	RS: Not reported
					Embolization in new territories: 4 (3.7%, n=107) in EVT arm
					PE: 1 (0.9%, n=107) in EVT arm
					No data for the medical arm
Olthuis et al[28]	Age ≥18 y, AIS, 6–24 from symptom onset or last well-known time, NIHSS score ≥2, baseline mRS 0–2, and TICA, M1, or proximal M2 occlusion	502	EVT and IAT+standard care	Standard care alone	RS: 15 (6%, n=255) vs 7(3%, n=247)
					RS: within the first 7 d: 4 (2%, n=255) vs 3 (1%, n=247)
					ACS: 0 (0%, n=255) vs 0 (0%, n=247)
Sarraj et al[29]	Age 18–85 y, AIS, symptom onset ≤24 h, ASPECTS 3–5 or CTP/DWI Core ≥50 mL and ICA or MCA occlusion	352	EVT+medical care	Medical care alone	RS: 3 (1.7%, n=178) vs 3 (1.7%, n=174)
					DVT: 2 (1.1%, n=178) vs 2 (1.1%, n=174)
					MI: 2 (1.1%, n=178) vs 3 (1.7%, n=174)
					PE: 4 (2.2%, n=178) vs 3 (1.7%, n=174)
Tao et al[30]	Age >18 y, AIS, symptom onset <12 h, NIHSS score ≥10 and BA occlusion	340	EVT (including intra/extracranial stenting, IAT, tirofiban used) plus standard care	Standard care alone	RS: 2 (0.9%, n=226) vs 1 (0.9%, n=114)
					NSTE: not reported
Yoo et al[31]	Age 18–85 y, AIS, symptom onset ≤24 h, NIHSS score ≥6, baseline mRS 0–1, and ASPECTS 2–5	300	EVT (including Intra/extracranial angioplasty and stenting, IAT) plus standard care	Standard care alone	RS: 10 (6.3%, n=158) vs 10 (7%, n=142)
					RIS: 3 (1.9%, n=158) vs 2 (1.4%, n=142)
					DVT: 16 (10.1%, n=158) vs 6 (4.2%, n=142)
					PE: 4 (2.5%, n=158) vs 5 (3.5%, n=142)
					MI: 1 (0.6%, n=158) vs 4 (2.8%, n=142)
Yoshimura et al[32]	Age ≥18 y, AIS, symptom onset ≤6 h, no FLAIR changes if symptoms onset 6–24 h or not known onset time, and ASPECTS 3–5	203	EVT (including intracranial/extracranial stenting)	Standard care	RS: 5 (5%, n=100) vs 7 (6.9%, n=102)
					RIS same as RS: 5 (5%, n=100) vs 7 (6.9%, n=102)

ACS indicates acute coronary syndrome; AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; BA, basilar artery; CTP, computed tomographic perfusion; DVT, deep vein thrombosis; DWI, diffusion-weighted imaging; EVT, endovascular thrombectomy; FDA, Food and Drug Administration; IAT, intra-arterial thrombolysis; ICA, internal carotid artery; IVT, intravenous thrombolysis; M1, first part of middle cerebral artery; M2, second part of middle cerebral artery; MCA, middle cerebral artery; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSTE, nonstroke thrombotic events; PE, pulmonary embolism; RIS, recurrent ischemic stroke; RS, recurrent stroke; TICA, terminal ICA; and tPA, tissue-type plasminogen activator.

Table 2. Characteristics of Included Studies Intravenous Thrombolysis Group

Author, y	Design	N	Intervention	Control	Primary outcomes
Albers et al[33]	Age 18–85 y, AIS, symptom onset 3–9 h, NIHSS score 4–24, and occlusion or high grade stenosis in proximal segments of MCA, ACA, or PCA	478	Desmoteplase	Placebo	RIS: 5 (2%, n=240) vs 5 (2%, n=238)
					NSTE: not reported
Albers et al[34]	Age ≥18 y, AIS, symptom onset: 4.5–24 h, baseline mRS score 0–2, NIHSS ≥5, and evidence of salvageable brain tissue on CT/MR perfusion imaging*	458	Tenecteplase±EVT	Placebo±EVT	RS: 1 (0.4%, n=228) vs 3 (1.3%, n=230)
Chen et al[35]	Age ≥18 y, AIS, symptom onset <4.5 h, and NIHSS score ≤5 with mild nondisabling AIS	719	Alteplase	DAPT	RS: 2 (0.6%, n=350) vs 1(0.3%, n=369)
Coutts et al[36]	Age ≥18 y, AIS, symptom onset within 12 h, NIHSS score 0–5, and minor ischemic stroke with proven occlusion	884	Tenecteplase	Standard care	RS: 15 (3%, n=452) vs 16 (4%, n=432)
					NSTE: not reported
Hacke et al[37]	Age 18–80 y, AIS, symptom onset within 6 h. Moderate to severe neurological deficit, and no major early infarct signs on initial brain CT scan	620	Alteplase	Standard care	RS: not reported
					MI: 4 (1.2%, n=309) vs 1 (0.3%, n=311)
					PE: 7 (2.2%, n=309) vs 8 (2.6%, n=311)
Sandercock et al[38]	All ages, AIS, symptom onset within 6 h,	3035	Alteplase	Standard care	RS: 24 (1.6%, n=1515) vs 23 (1.5%, n=1520)
					RIS: 21 (1.4%, n=1515) vs 20 (1.3%, n=1520)
					MI: 23 (1.6%, n=1515) vs 23 (1.5%, n=1520)
Khatri et al[39]	Age ≥18 y, AIS, symptom onset within 6 h, NIHSS 0–5 with mild nondisabling stroke	313	IV alteplase+oral placebo	Oral aspirin 325 plus IV placebo	RS: 5 (3.2%, n=156) vs 6 (4.0%, n=157)
Ma et al[40]	AGe ≥18 y, AIS, symptom onset 4.5 to 9 h or within 9 h from the midpoint of sleep, NIHSS score 4–26, baseline mRS score: 0–1 and perfusion imaging available	225	Alteplase	Placebo	RS: 1(0.9%, n=113) vs 1 (0.9%, n=112)
					ACS: 1(0.88%, n=113) vs 5 (4.46%, n=112)
					DVT/PE: 1(0.88%, n=113) vs 1 (0.89%, n=112)
Roaldsen et al[41]	Age ≥18 y or older, wake up AIS, symptom onset within 4·5 h of awakening and NIHSS ≥3 or aphasia	578	Tenecteplase	Standard care	RIS: 4 (1%, n=288) vs 2 (1%, n=290)
					ACS: 2 (1%, n=288) vs 2 (1%, n=290)
					DVT/PE: 4 (1%, n=288) vs 4 (1%, n=290)
Thomalla et al 2018[42]	Age ≥18 y, AIS of unknown time of onset, measurable disabling neurological deficit, and decision based on DWI/FLAIR mismatch on MRI	503	Alteplase	Placebo	RIS: 17 (6.8%, n=254) vs 8 (3.3%, n=249)
					ACS: 9 (3.6%, n=254) vs 10 (4.1%, n=249

ACS indicates acute coronary syndrome; AIS, acute ischemic stroke; CTP, computed tomography; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; DWI, diffusion-weighted imaging; EVT, endovascular thrombectomy; MCA, middle cerebral artery; MI, myocardial infarction; MR, magnetic resonance; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSTE, nonstroke thrombotic events; PE, pulmonary embolism; RIS, recurrent ischemic stroke; and RS, recurrent stroke.

*Initial ischemic core volume of <70 mL, a ratio of the volume of ischemic tissue to the initial infarct volume of at least 1.8, and an absolute volume of potentially reversible ischemia (penumbra) of at least 15 mL.

NSTE, along with corresponding 95% CIs, to quantify the effect of reperfusion therapies compared with the best medical therapy at 90 days. Zero cells were adjusted by 0.5. Heterogeneity was assessed using the I^2 statistic, with values of 0% to 40% indicating low heterogeneity, 30% to 60% indicating moderate heterogeneity, and 50% to 90% indicating substantial heterogeneity. The risk ratio was calculated from the log risk ratio, along with a 95% CI. The continuity correction approach, which adds 0.5 to cells with zero events, may bias the results towards the null. Thus, an alternative meta-analysis model was

tested using a random-effects generalized linear mixed model for a binary outcome, along with an adaptive Gauss-Hermite quadrature estimation method. Since there was no change in the results, we report log RR and RR. The generalized linear mixed model results are reported in Table S3. A visual abstract was created to summarize the key findings of the meta-analysis. Statistical analyses were performed using STATA 18.0 BE (StataCorp LLC, College Station, TX).

RESULTS

A total of 170 studies were screened by 2 reviewers from the study period (2013–2024), and of these, 29 studies were included in the systematic review and 25 studies in the meta-analysis. In the endovascular therapy group, 15 studies (n=4898) reported 252 (5%) early recurrent strokes at 90 days; 14 studies (n=4033) reported 128 (2.7%) NSTE (Table 1)[15–32,43] in the same time frame. In the IVT alone group, 9 studies (n=7193) reported 140 (1.9%) early recurrent strokes at 90 days; 5 studies (n=4961) reported 105 (2.1%) NSTE (Table 2)[33–42] at 90 days.

Risk of Bias of Assessment

Selection Bias

All studies (100%) had a low risk in the randomization process, indicating adequate randomization and allocation concealment.

Performance Bias

Across studies, 56.3% were judged at low risk for deviations from intended interventions, whereas 43.7% had some concerns, reflecting variability in blinding of participants and personnel.

Attrition Bias

Missing outcome data were consistently well handled, with 100% of studies rated as low risk.

Detection Bias

Regarding measurement of the outcome, 92.4% of studies were at low risk and 7.6% had some concerns, suggesting generally robust blinding of outcome assessors, though not universal.

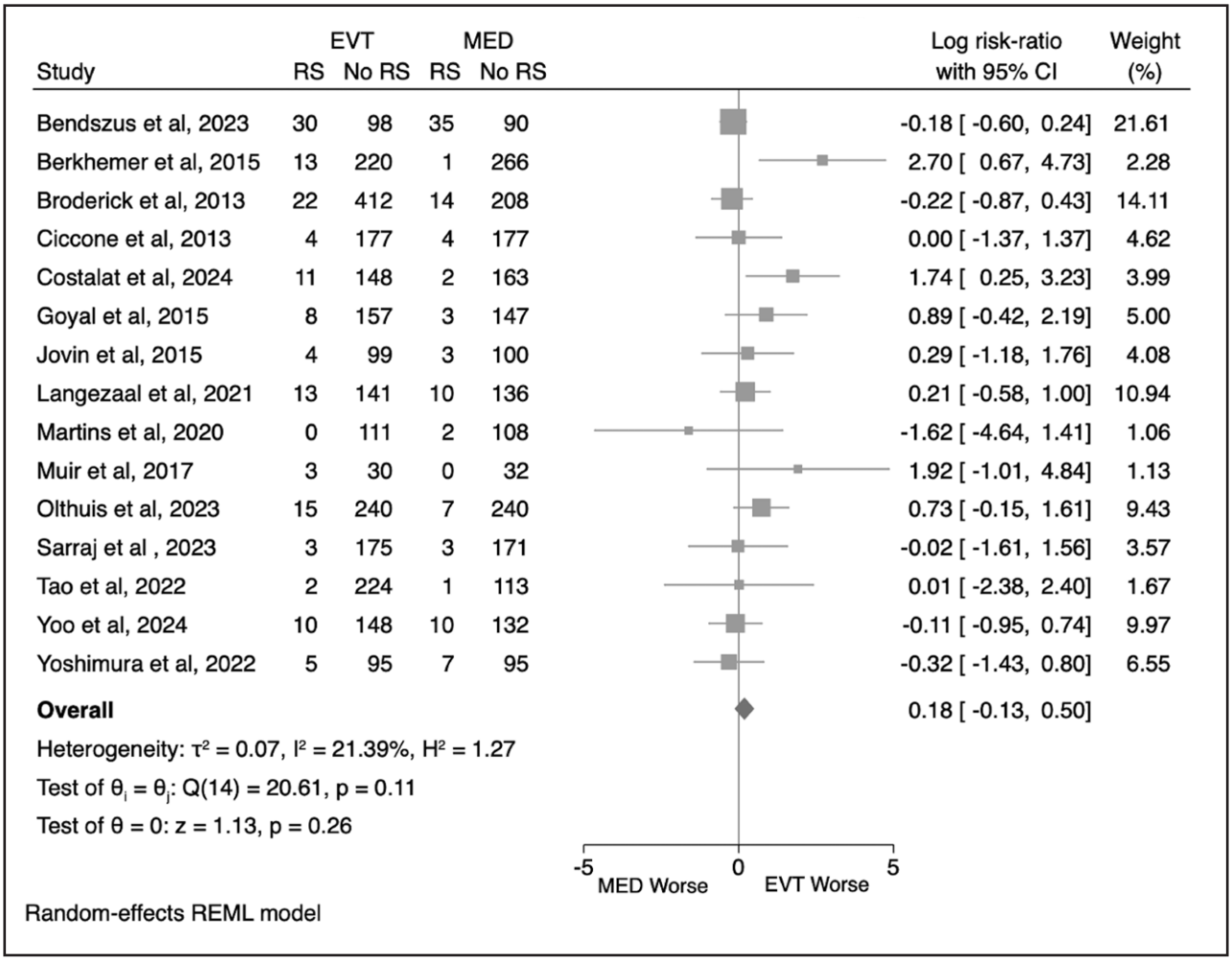

Figure 2. Forest plot for acute ischemic stroke between endovascular thrombectomy (EVT) and best medical therapy (MED) with the occurrence of recurrent stroke (RS) within 90 days of symptom onset.
REML indicates restricted maximum likelihood.

ORIGINAL CONTRIBUTION

Reporting Bias

For selection of the reported result, 87.1% of studies were low risk, and 12.9% had some concerns, pointing to occasional selective reporting.

Overall Bias

Combining domains, 49% of studies were at low risk overall, and 51% had some concerns; none were rated at high risk (EVT: Table S1; Figures S1 and S2 and IVT: Table S2; Figures S3 and S4).

Overall, this synthesis indicates that most included studies were methodologically rigorous, with a predominance of low risk across domains, supporting the reliability and robustness of the findings.

Measures of Effect

90-Day Recurrent Stroke

EVT Group

In the 15 RCTs comparing EVT with MED, early recurrent stroke occurred in 5.5% (143/2618) of the EVT group compared with 4.5% (102/2280) in the MED group. This yielded a log RR of 0.18 (95% CI, −0.13 to 0.50) and RR, 1.2 (95% CI, 0.9–1.6), indicating no difference between groups (Table S3; Figure 2).

IVT Alone Group

For the 9 RCTs comparing IVT with MED, early recurrent stroke occurred in 2% (73/3615) of the IVT group compared with 1.8% (66/3578) in the MED group, with a log RR of 0.11 (95% CI, −0.22 to 0.45), and RR 1.1 (95% CI, 0.8–1.5) also indicating no difference between groups (Figure 3).

Nonstroke Thrombotic Events

EVT Group

Among the 14 RCTs assessing NSTE, rates were 3.1% (62/2024) in the EVT group compared with 3.1% (62/2009) in the MED group, yielding a log RR of 0.01 (95% CI, −0.35 to 0.37) and RR 1 (95% CI, 0.7–1.4; Figure 4) indicating no difference between groups.

IVT Alone Group

In the 5 RCTs comparing IVT with MED, the rates of NSTE were 2% (51/2479) in the IVT group and 2.2% (54/2482) in the MED group, with log RR of −0.05 (95% CI, −0.43 to 0.34), and RR, 0.9 (95% CI, 0.6–1.4) indicating no difference between groups (Figure 5).

DISCUSSION

In this meta-analysis, we demonstrate that the occurrence of thrombotic events postreperfusion therapy is infrequent. Furthermore, there is no difference in the occurrence of thrombotic events postreperfusion therapy compared with standard medical management. Although a prior meta-analysis of EVT trials reported a 3-fold higher risk of recurrent stroke within 90 days in EVT-treated patients compared with controls (5% versus

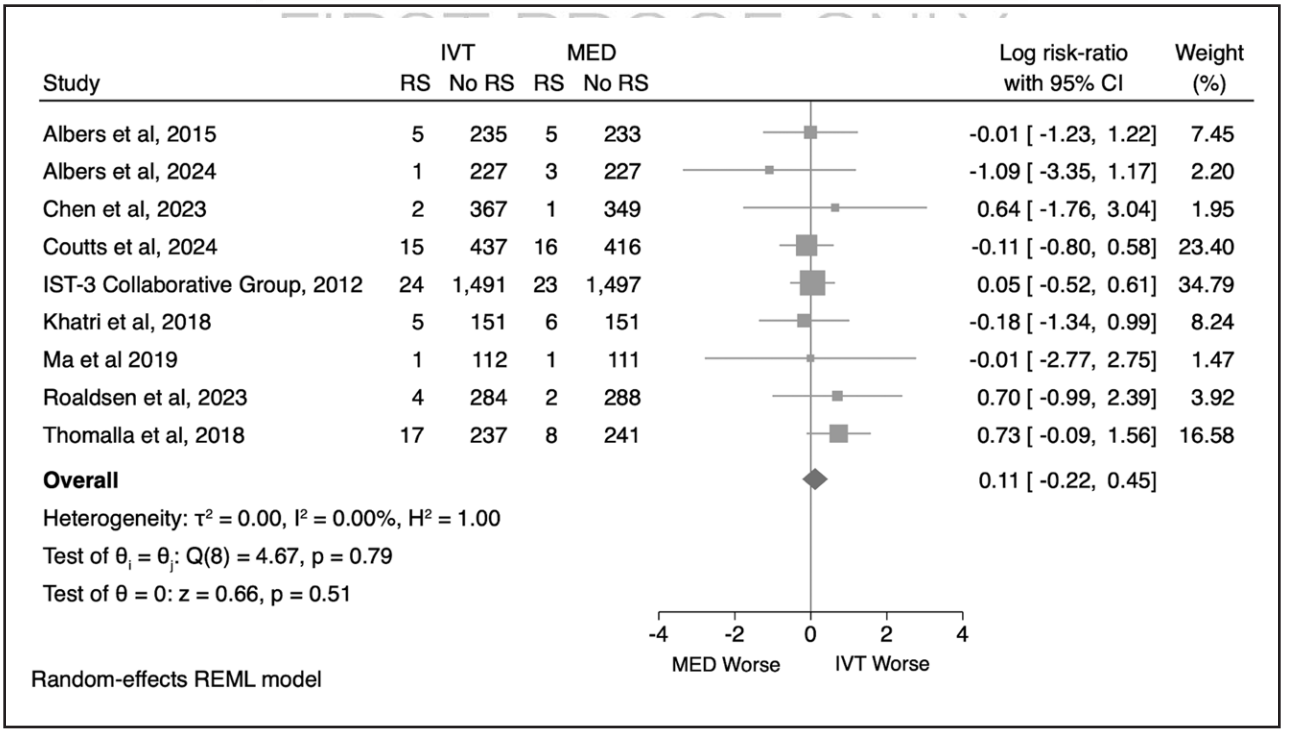

Figure 3. Forest plot for acute ischemic stroke between intravenous thrombolysis (IVT) and best medical therapy (MED) with the occurrence of recurrent stroke (RS) within 90 days of symptom onset.
REML indicates restricted maximum likelihood.

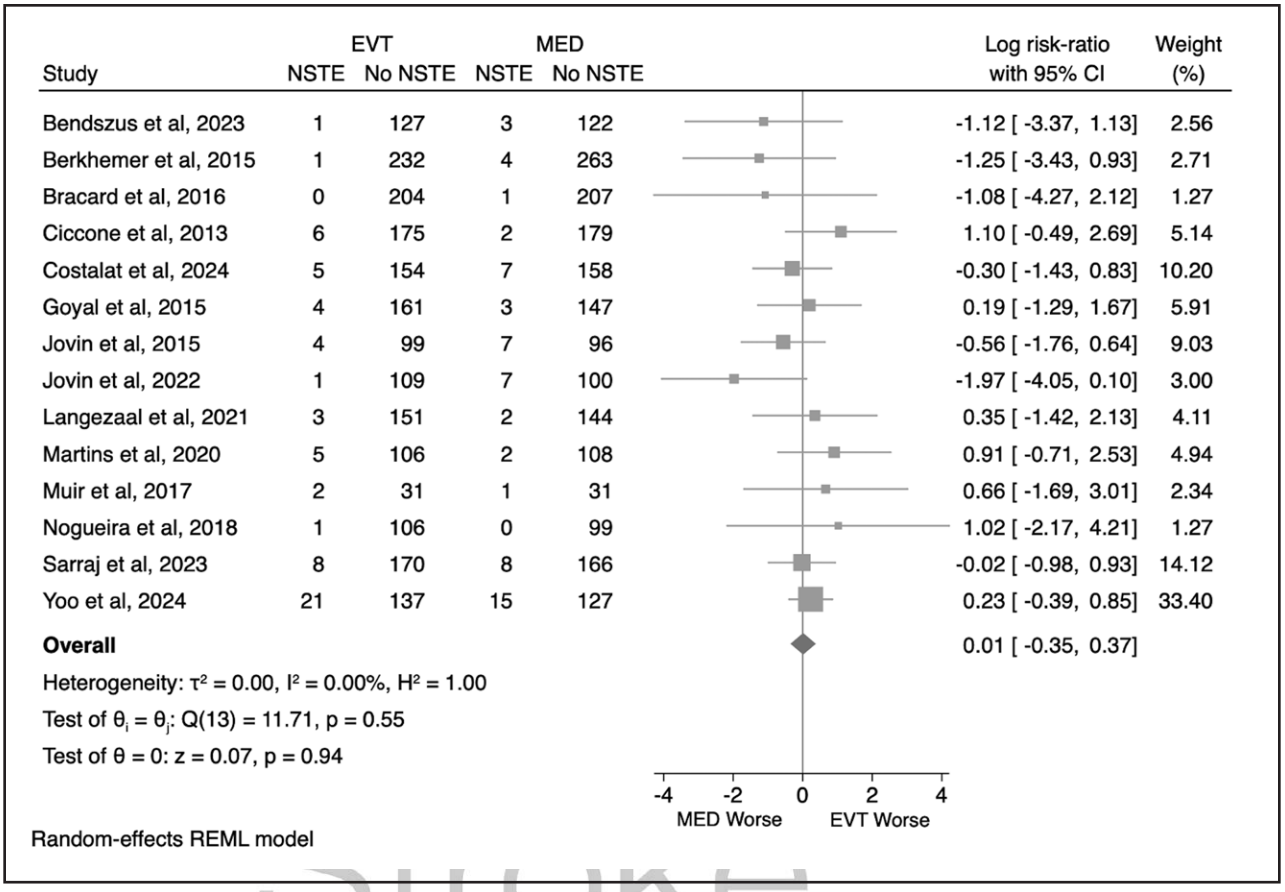

Figure 4. Forest plot for acute ischemic stroke between endovascular thrombectomy (EVT) and best medical therapy (MED) with the occurrence of nonstroke thrombotic events (NSTE), including acute coronary syndrome, myocardial infarction, ST-elevation myocardial infarction (STEMI), non-ST–elevation myocardial infarction (NSTEMI), pulmonary thromboembolism, and deep venous thrombosis within 90 days of symptom onset.
REML indicates restricted maximum likelihood.

1.3%), our analysis found no significant difference in early recurrent stroke rates between EVT and medical management (5.5% versus 4.5%).[10] This discrepancy may be due to: a smaller sample size (n=1021) in the previous meta-analyses compared with the current meta-analyses (n=4898), the previous consisted only of anterior circulation stroke within the first 6 hours; however, our meta-analysis consists of a broader inclusion of trials with symptom onset up to 24 hours, basilar artery occlusion, and large hemispheric infarction.

An observational study by Hsueh et al[9] observed a recurrent stroke rate of 8.5% within 30 days in patients treated with EVT for large vessel occlusions. In contrast, another observational study examining IVT reported a much lower early recurrent ischemic event rate of 2.6%, which is closer to the rates observed in our analysis.[44] However, the majority of patients had atrial fibrillation (83.3%). One hypothesis for recurrent stroke following EVT involves mechanical manipulation of the artery, which may cause embolization of thrombotic material, potentially increasing the risk of new ischemic events. In the ESCAPE NA1 (Safety and Efficacy of Nerinetide [NA-1] in subjects Undergoing Endovascular Thrombectomy for Stroke) trial, infarction in a new territory was observed in 9.3%, and one-third were >20 mm in size.[45] These infarcts in new territory were associated with poorer outcomes. In the current meta-analysis, there was an increased risk of symptomatic recurrent stroke in EVT-treated patients. However, it is challenging to differentiate between early neurological deterioration due to the progression of the stroke and recurrent stroke, particularly in the first 72 hours.

The risk of recurrent stroke was higher in the EVT group (5%) compared with the IVT alone group (1.9%). The differences in stroke severity and the underlying stroke cause may partially explain this. EVT is a procedure that is most commonly performed for AIS and large-vessel occlusions, which are often caused by a cardioembolic source or large artery atherosclerosis. These causes are associated with a higher risk of early recurrent strokes. In contrast, IVT is frequently administered to all patients with stroke (with and without large-vessel intracranial occlusions) and those with small-vessel disease, which tends to carry a relatively lower risk for early

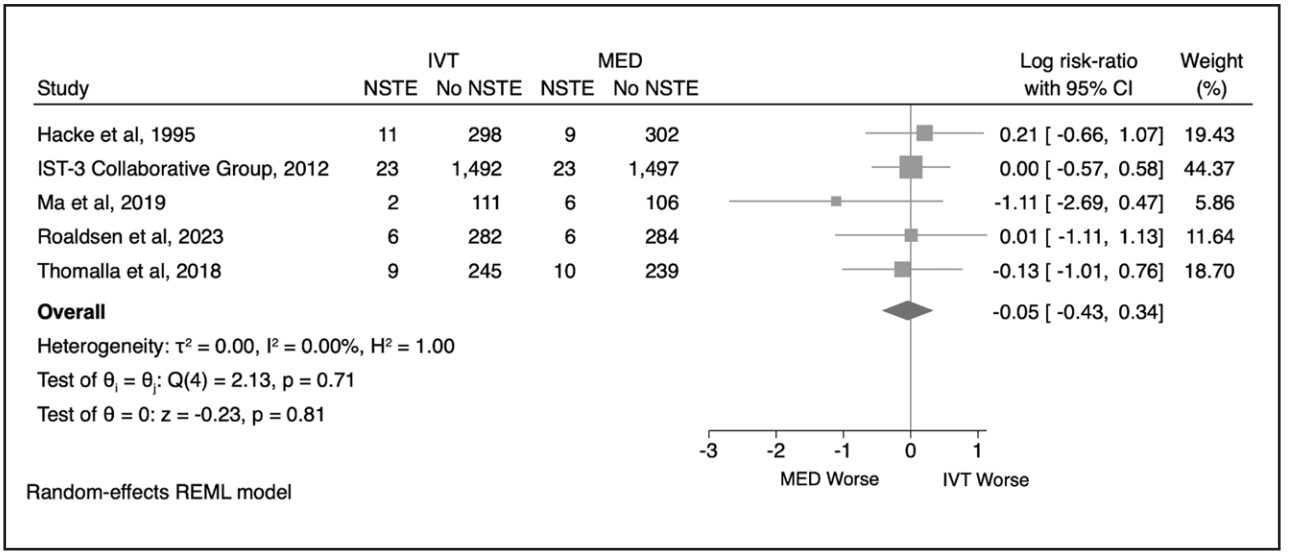

Figure 5. Forest plot for acute ischemic stroke between intravenous thrombolysis (IVT) and best medical therapy (MED) with the occurrence of nonstroke thrombotic events (NSTE), including acute coronary syndrome, myocardial infarction, ST-elevation myocardial infarction (STEMI), non-ST–elevation myocardial infarction (NSTEMI), pulmonary thromboembolism, and deep venous thrombosis within 90 days of symptom onset.
REML indicates restricted maximum likelihood.

recurrent stroke. It is important to acknowledge that the 90-day definition of early recurrent stroke may include events not directly attributable to EVT-specific mechanisms, as procedural risks, such as reocclusion or distal embolism, are more likely to contribute to recurrence in the immediate postintervention period, whereas later events may reflect broader systemic or patient-related factors.

The occurrence of NSTE was similar between the groups, suggesting that reperfusion therapy, whether EVT or IVT, does not significantly increase the risk of thrombotic complications such as MI, pulmonary embolism, or deep vein thrombosis. This aligns with the results of several observational studies, which report a low incidence of thrombotic events in the acute phase following reperfusion therapy.[44] Similarly, IVT alone is associated with a low incidence of acute myocardial injury, although the long-term effects on thrombotic events remain unclear.[46] In contrast, another observational study showed a high prevalence of deep vein thrombosis in patients with ischemic stroke within 10 days of undergoing thrombectomy, with an occurrence rate of 27.3% (67/245).[47]

Our study has several limitations. One key limitation is the exclusion of studies that did not report thrombotic events, which reduced the sample size and may have limited the power of our analysis in detecting minor differences in the occurrence of early recurrent strokes and NSTE. Additionally, there may be an underreporting of recurrent stroke, particularly in larger strokes. Another important limitation is the variability in the definition of recurrent stroke across the included studies. This is particularly relevant for thrombectomy trials, where recurrent stroke may reflect procedural complications, evolution of the index stroke, or true recurrence, potentially contributing to heterogeneity in the reported outcomes. Furthermore, our meta-analysis included studies with diverse methodologies, patient populations, and treatment protocols, which may introduce bias and limit the generalizability of our findings. Lastly, the reliance on 90-day follow-up data may not fully capture the long-term risk of recurrent stroke or other thrombotic events.

Since we do not have patient-level data, we could not perform further subgroup analyses. However, some studies suggest that the role of endovascular therapy in patients with symptomatic intracranial stenosis remains complex, with evidence pointing to an increased risk of short-term stroke and death when compared with medical therapy alone, particularly in the early phase of intervention.[48] New evidence from the BASIS (Balloon Angioplasty for Symptomatic Intracranial Artery Stenosis) trial suggests that in patients with symptomatic intracranial stenosis, balloon angioplasty plus aggressive medical management significantly lowers the risk of any stroke or death within 30 days, and ischemic stroke or revascularization beyond 30 days up to 12 months.[49] However, the early risk of stroke or death within 30 days must be considered in clinical practice. Further trials are needed to confirm or challenge these findings, particularly regarding the role of EVT in symptomatic intracranial stenosis and its long-term benefits.

To better prevent recurrent strokes after EVT or IVT, future research should focus on the timing and type of antithrombotic therapy initiated postprocedure. A clinical trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06638151) will explore whether single antiplatelet treatment is as effective as dual antiplatelet

therapy immediately after reperfusion. Investigating the optimal duration of treatment, especially for large vessel occlusion strokes postreperfusion therapy, could help reduce recurrent stroke risk. Tailoring treatments based on stroke subtype may also improve outcomes.

CONCLUSIONS

Our meta-analysis suggests that neither EVT nor IVT increases the risk of early recurrent stroke or NSTE within 90 days when compared with MED. However, the possibility of underreporting in larger strokes and differences in stroke severity between EVT and IVT groups warrant further exploration. It is important to note that the observed neutrality in our results may reflect insufficient data or variability in participant characteristics that could influence outcomes. Prospective, large-scale studies with more comprehensive long-term follow-up are necessary to better understand the recurrence of stroke and thrombotic events following reperfusion therapies.

ARTICLE INFORMATION

Received January 11, 2025; final revision received September 1, 2025; accepted October 1, 2025.

Affiliations

Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Canada (R.A.A., K.S., S.K.C., A.S., B.H.B., M.K.). Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India (P.N.S.). Department of Clinical Neurosciences, University of Calgary, AB, Canada (M.A.). Division of Clinical Science, Health Sciences North, Northern Ontario School of Medicine, Sudbury, Canada (A.D.). School of Cardiovascular and Metabolic Health, University of Glasgow, United Kingdom (J.D.). Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, South Korea (S.-I.S.). Division of Neurology, University of Montreal, QC, Canada (L.C.G.).

Sources of Funding

None.

Disclosures

Dr Gioia provided consultant services for Bayer; grants from AstraZeneca Canada; compensation from Servier Pharmaceuticals LLC for consultant services; grants from Fonds de Recherche du Québec–Santé; and compensation from Heart and Stroke Foundation of Canada for other services. Dr Kate is affiliated with the University of Alberta. The other authors report no conflicts.

Supplemental Material

PRISMA 2020 Checklist
EVT Risk of Bias Excel: Print (ITT)
IVT Risk of Bias Excel: Print (ITT)
Table S3

REFERENCES

1. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke – a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2021;30:105935. doi: 10.1016/j.jstrokecerebrovasdis.2021.105935
2. Stahmeyer JT, Stubenrauch S, Geyer S, Weissenborn K, Eberhard S. The frequency and timing of recurrent stroke: an analysis of routine health insurance data. *Dtsch Arztebl Int*. 2019;116:711–717. doi: 10.3238/arztebl.2019.0711
3. Kang K, Park TH, Kim N, Jang MU, Park SS, Park JM, Ko Y, Lee SJ, Lee KB, Lee J, et al. Recurrent stroke, myocardial infarction, and major vascular events during the first year after acute ischemic stroke: The multicenter prospective observational study about recurrence and its determinants after acute ischemic stroke I. *J Stroke Cerebrovasc Dis*. 2016;25:656–664. doi: 10.1016/j.jstrokecerebrovasdis.2015.11.036
4. Arsava EM, Kim GM, Oliveira-Filho J, Gungor L, Noh HJ, De Jesus Lordelo M, Avery R, Maier IL, Ay H. Prediction of early recurrence after acute ischemic stroke. *JAMA Neurol*. 2016;73:396–401. doi: 10.1001/jamaneurol.2015.4949
5. Rinde LB, Småbrekke B, Mathiesen EB, Løchen ML, Njølstad I, Hald EM, Wilsgaard T, Brækkan SK, Hansen JB. Ischemic stroke and risk of venous thromboembolism in the general population: the Tromsø study. *J Am Heart Assoc*. 2016;5:e004311. doi: 10.1161/JAHA.116.004311
6. Mihalovic M, Mikulenka P, Línková H, Neuberg M, Štětkářová I, Peisker T, Lauer D, Tousek P. Prevalence of myocardial injury in patients after acute ischaemic stroke according to standard criteria. *Eur Heart J Suppl*. 2023;25:E3–E9. doi: 10.1093/eurheartjsupp/suad104
7. Heran M, Lindsay P, Gubitz G, Yu A, Ganesh A, Lund R, Arsenault S, Bickford D, Derbyshire D, Doucette S, et al. Canadian stroke best practice recommendations: acute stroke management, 7th edition practice guidelines update, 2022. *Can J Neurol Sci*. 2024;51:1–31. doi: 10.1017/cjn.2022.344
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
9. Hsueh SJ, Chen CH, Yeh SJ, Lin YH, Tsai LK, Lee CW, Tang SC, Jeng JS. Early recurrence of ischemic stroke in patients receiving endovascular thrombectomy. *J Formos Med Assoc*. 2021;120:854–862. doi: 10.1016/j.jfma.2020.09.007
10. Emprechtinger R, Piso B, Ringleb PA. Thrombectomy for ischemic stroke: meta-analyses of recurrent strokes, vasospasms, and subarachnoid hemorrhages. *J Neurol*. 2017;264:432–436. doi: 10.1007/s00415-016-8205-1
11. Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke–heart syndrome: recent advances and challenges. *J Am Heart Assoc*. 2022;11:26528. doi: 10.1161/JAHA.122.026528
12. Flach C, Muruet W, Wolfe CDA, Bhalla A, Douiri A. Risk and secondary prevention of stroke recurrence: a population-base cohort study. *Stroke*. 2020;51:2435–2444. doi: 10.1161/STROKEAHA.120.028992
13. Mazighi M, Meseguer E, Labreuche J, Amarenco P. Bridging therapy in acute ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2012;43:1302–1308. doi: 10.1161/STROKEAHA.111.635029
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71
15. Bendszus M, Bonekamp S, Herweh C, Möhlenbruch M, Ulfert C, Vollherbst DF, Ringleb PA, Schönenberger S, Wick W, Fiehler J, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. *Lancet*. 2023;402:1753–1763. doi: 10.1016/S0140-6736(23)02032-9
16. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJH, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
17. 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;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
18. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, et al; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368:893–903. doi: 10.1056/NEJMoa1214300
19. Costalat V, Jovin TG, Albucher JF, Cognard C, Henon H, Nouri N, Gory B, Richard S, Marnat G, Sibon I, et al; LASTE Trial Investigators. Trial of thrombectomy for stroke with a large infarct of unrestricted size. *N Engl J Med*. 2024;390:1677–1689. doi: 10.1056/NEJMoa2314063
20. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905

21. Jovin TG, Li C, Wu L, Wu C, Chen J, Jiang C, Shi Z, Gao Z, Song C, Chen W, et al; BAOCHE Investigators. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med.* 2022;387:1373–1384. doi: 10.1056/NEJMoa2207576
22. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
23. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, et al; MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med.* 2013;368:914–923. doi: 10.1056/NEJMoa1212793
24. Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, de Carvalho JJF, Lima FO, Dippel DWJ, van der Lugt A, Lo RTH, Boiten J, Lycklama à Nijeholt GJ, et al; BASICS Study Group. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med.* 2021;384:1910–1920. doi: 10.1056/NEJMoa2030297
25. Martins SO, Mont'Alverne F, Rebello LC, Abud DG, Silva GS, Lima FO, Parente BSM, Nakiri GS, Faria MB, Frudit ME, et al; RESILIENT Investigators. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med.* 2020;382:2316–2326. doi: 10.1056/NEJMoa2000120
26. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, et al; PISTE Investigators. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry.* 2016;88:38–44. doi: 10.1136/jnnp-2016-314117
27. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* 2018;378:11–21. doi: 10.1056/NEJMoa1706442
28. Olthuis SGH, Pirson FAV, Pinckaers FME, Hinsenveld WH, Nieboer D, Ceulemans A, Knapen RRMM, Robbe MMQ, Berkhemer OA, van Walderveen MAA, et al. Endovascular treatment versus no endovascular treatment after 6–24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial. *Lancet.* 2023;401:1371–1380. doi: 10.1016/s0140-6736(23)00575-5
29. Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, et al; SELECT2 Investigators. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med.* 2023;388:1259–1271. doi: 10.1056/NEJMoa2214403
30. Tao C, Nogueira RG, Zhu Y, Sun J, Han H, Yuan G, Wen C, Zhou P, Chen W, Zeng G, et al; ATTENTION Investigators. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med.* 2022;387:1361–1372. doi: 10.1056/NEJMoa2206317
31. Yoo AJ, Zaidat OO, Sheth SA, Rai AT, Ortega-Gutierrez S, Given CA, Zaidi SF, Grandhi R, Cuellar H, Mokin M, et al; Writing Committee for the TESLA Investigators. Thrombectomy for stroke with large infarct on noncontrast CT: the TESLA randomized clinical trial. *JAMA.* 2024;332:1355–1366. doi: 10.1001/jama.2024.13933
32. Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, Matsumaru Y, Matsumoto Y, Kimura K, Takeuchi M, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med.* 2022;386:1303–1313. doi: 10.1056/NEJMoa2118191
33. Albers GW, von Kummer R, Truelsen T, Jensen JKS, Ravn GM, Grønning BA, Chabriat H, Chang KC, Davalos AE, Ford GA, et al; DIAS-3 Investigators. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Neurol.* 2015;14:575–584. doi: 10.1016/S1474-4422(15)00047-2
34. Albers GW, Jumaa M, Purdon B, Zaidi SF, Streib C, Shuaib A, Sangha N, Kim M, Froehler MT, Schwartz NE, et al; TIMELESS Investigators. Tenecteplase for stroke at 4.5 to 24 hours with perfusion-imaging selection. *N Engl J Med.* 2024;390:701–711. doi: 10.1056/NEJMoa2310392
35. Chen HS, Cui Y, Zhou ZH, Zhang H, Wang LX, Wang WZ, Shen LY, Guo LY, Wang EQ, Wang RX, et al; ARAMIS Investigators. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA.* 2023;329:2135–2144. doi: 10.1001/jama.2023.7827
36. Coutts SB, Ankolekar S, Appireddy R, Arenillas JF, Assis Z, Bailey P, Barber PA, Bazan R, Buck BH, Butcher KS, et al; TEMPO-2 investigators. Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial. *Lancet.* 2024;403:2597–2605. doi: 10.1016/S0140-6736(24)00921-8
37. Hacke W. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;274:1017–1025.
38. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, et al; IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third International Stroke Trial [IST-3]): a randomised controlled trial. *Lancet.* 2012;379:2352–2363. doi: 10.1016/S0140-6736(12)60768-5
39. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN, Starr M, Mejilla J, Broderick J, Chatterjee A, Jauch EC, Levine SR, et al; PRISMS Investigators. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. *JAMA.* 2018;320:156–166. doi: 10.1001/jama.2018.8496
40. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med.* 2019;380:1795–1803. doi: 10.1056/NEJMoa1813046
41. Roaldsen MB, Eltoft A, Wilsgaard T, Christensen H, Engelter ST, Indredavik B, Jatužis D, Karelis G, Kõrv J, Lundström E, et al; TWIST Investigators. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. *Lancet Neurol.* 2023;22:117–126. doi: 10.1016/S1474-4422(22)00484-7
42. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho T-H, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med.* 2018;379:611–622. doi: 10.1056/NEJMoa1804355
43. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E; SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. *N Engl J Med.* 2013;368:904–913. doi: 10.1056/NEJMoa1213701
44. Awadh M, MacDougall N, Santosh C, Teasdale E, Baird T, Muir KW. Early recurrent ischemic stroke complicating intravenous thrombolysis for stroke: incidence and association with atrial fibrillation. *Stroke.* 2010;41:1990–1995. doi: 10.1161/STROKEAHA.109.569459
45. Singh N, Cimflova P, Ospel JM, Kashani N, Marko M, Mayank A, Nogueira RG, Mctaggart RA, Demchuk AM, Poppe AY, et al; ESCAPE-NA1 Trial Investigators. Infarcts in a new territory: insights from the ESCAPE-NA1 trial. *Stroke.* 2023;54:1477–1483. doi: 10.1161/STROKEAHA.122.042200
46. Adatia S, Sanghani S, Sanzgiri P, Chauhan V, Hastak S. Acute myocardial infarction following intravenous tissue plasminogen activator for acute ischemic stroke: an unknown danger. *Ann Indian Acad Neurol.* 2010;13:64–66. doi: 10.4103/0972-2327.61282
47. Han L, Yang JM, Qian WY, Xu XP, Tung TH, Liu Y, Wang F. Risk factors for lower extremity deep vein thrombosis in acute stroke patients following endovascular thrombectomy: a retrospective cohort study. *Front Neurol.* 2023;14:1249365. doi: 10.3389/fneur.2023.1249365
48. Luo J, Wang T, Yang K, Wang X, Xu R, Gong H, Zhang X, Wang J, Yang R, Gao P, et al. Endovascular therapy versus medical treatment for symptomatic intracranial artery stenosis. *Cochrane Database Syst Rev.* 2023;2023:CD013267. doi: 10.1002/14651858.CD013267.pub3
49. Sun X, Deng Y, Zhang Y, Yang M, Sun D, Nguyen TN, Tong X, Peng G, Liu A, Xu Y, et al; BASIS Investigators. Balloon angioplasty vs medical management for intracranial artery stenosis: the BASIS randomized clinical trial. *JAMA.* 2024;332:1059–1069. doi: 10.1001/jama.2024.12829