RESEARCH ARTICLE

# Meta-Analysis of Randomized Controlled Trials on IV Thrombolysis in Patients With Minor Acute Ischemic Stroke

Mohamed F. Doheim,[1] Thanh N. Nguyen,[2] Yunyun Xiong,[3] Hui-Sheng Chen,[4] Nirav R. Bhatt,[1] Yongjun Wang,[3] and Raul G. Nogueira[1,5]

*Neurology*® 2025;105:e213863. doi:10.1212/WNL.0000000000213863

**Correspondence**
Dr. Nogueira
nogueirarg@upmc.edu
or Dr. Doheim
doheimmf@upmc.edu

MORE ONLINE

**Supplementary Material**

## Abstract

### Background and Objectives

The therapeutic efficacy and safety of IV thrombolysis (IVT) for patients with minor strokes remain a subject of significant debate and uncertainty. This meta-analysis aimed to assess the comparative effectiveness and safety of IVT vs nonthrombolytic standard of care (NT-SC) in minor strokes, focusing exclusively on data from randomized controlled trials (RCTs).

### Methods

A comprehensive literature search was conducted to identify RCTs evaluating IVT in minor stroke, defined as a NIH Stroke Scale (NIHSS) score ≤5. The primary outcome was excellent functional recovery, defined as a modified Rankin Scale (mRS) score of 0–1 at 90 days. Secondary outcomes included functional independence (mRS 0–2 at 90 days) and safety end points, including 90-day mortality, recurrent stroke, symptomatic intracranial hemorrhage (sICH), and any ICH. The study was registered with PROSPERO (CRD42024621714).

### Results

The primary analysis included data from 4 RCTs that exclusively enrolled patients with minor stroke (N = 3,364; age range: 56–80 years). Secondary analyses incorporated post hoc and subgroup data on patients with minor stroke from earlier RCTs. In the primary analysis, IVT was not significantly associated with higher odds of excellent functional recovery at 90 days compared with NT-SC (mRS 0–1; odds ratio [OR] 0.85, 95% CI 0.70–1.03). IVT was significantly associated with lower odds of achieving 90-day functional independence (mRS 0–2; OR 0.71, 95% CI 0.55–0.91) and higher odds of both sICH (OR 5.22, 95% CI 1.76–15.48) and 90-day mortality (OR 2.40, 95% CI 1.23–4.67) compared with NT-SC. Subgroup analysis showed a nonsignificant association of IVT with odds of excellent functional recovery across both groups with disabling symptoms (OR 0.84, 95% CI 0.38–1.88) and nondisabling symptoms (OR 0.82, 95% CI 0.66–1.03). The pooled analysis, which incorporated nonoverlapping subgroups and post hoc data, yielded consistent findings.

### Discussion

The findings suggest that IVT does not confer improved functional outcomes among patients with minor strokes and can be associated with higher odds of sICH and mortality at 90 days compared with NT-SC. Since most of the included patients presented with nondisabling minor strokes, additional studies on patients with mildly disabling symptoms are warranted.

## Introduction

Stroke remains a predominant cause of long-term disability and mortality worldwide, with minor ischemic strokes—commonly defined as a NIH Stroke Scale (NIHSS) score ≤5—

[1]UPMC Stroke Institute, Department of Neurology, University of Pittsburgh School of Medicine, PA; [2]Departments of Neurology and Radiology, Boston Medical Center, MA; [3]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, China; [4]Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China; and [5]UPMC Stroke Institute, Department of Neurosurgery, University of Pittsburgh School of Medicine, PA.

## Glossary

**AIS** = acute ischemic stroke; **ATLANTIS** = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; **DAPT** = dual antiplatelet therapy; **ECASS** = European Cooperative Acute Stroke Study; **EVT** = endovascular thrombectomy; **IPD** = individual participant data; **IST-3** = third International Stroke Trial; **IVT** = IV thrombolysis; **LVO** = large-vessel occlusion; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **NT-SC** = nonthrombolytic standard of care; **OHS** = Oxford Handicap Scale; **OR** = odds ratio; **RCT** = randomized controlled trial; **sICH** = symptomatic intracranial hemorrhage; **SITS-MOST** = the Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

comprising over 50% of acute ischemic stroke (AIS) presentations.[1-3] Despite their seemingly mild severity, up to one-third of patients with minor strokes progress to functional impairment within 90 days due to recurrent or evolving stroke pathology.[3-6]

The management of minor AIS poses significant clinical challenges, particularly regarding the utility of IV thrombolysis (IVT), which, while well-established for more severe strokes, lacks robust evidence in this subgroup. Current guidelines recommend IVT for minor strokes with disabling deficits.[7,8] This recommendation is primarily based on an exploratory subgroup analysis from an individual participant data (IPD) meta-analysis of 9 randomized controlled trials (RCTs) comparing alteplase IVT to placebo or open control for patients with NIHSS 0–4.[9] Moreover, the third International Stroke Trial (IST-3) demonstrated a benefit of IVT for patients presenting within 6 hours of stroke onset, with a greater benefit observed in those with higher NIHSS scores and a less pronounced benefit for patients with minor stroke symptoms.[10] Interestingly, positive findings supporting IVT for minor AIS have not been consistently replicated in large cohort studies conducted in real-world settings.[4,5,11,12] In addition, there is growing emphasis on distinguishing disabling from nondisabling symptoms in minor strokes.[13,14]

Previous meta-analyses sought to provide definitive evidence but had conflicting outcomes and increased uncertainty due to their reliance on observational studies and insufficiently robust analyses.[12,15,16] To address these issues, this systematic review and meta-analysis exclusively included data from RCTs to evaluate the safety and efficacy of IVT compared with nonthrombolytic standard of care (NT-SC) in minor AIS.

# Methods

## Standard Protocol Approvals and Registrations

This systematic review and meta-analysis was conducted in accordance with the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[17] The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure transparent and standardized reporting.[18] The protocol for this review was registered in the PROSPERO database as CRD42024621714.

## Search Strategy

We conducted a systematic search of the PubMed, ClinicalTrials.gov, Cochrane Library, and Web of Science databases, covering all records from January 1995 to December 2024. The search strategy incorporated a combination of keywords, including minor stroke, acute ischemic stroke, thrombolysis, intravenous thrombolysis, tissue plasminogen activator, alteplase, tenecteplase, and prourokinase, to capture all relevant literature, as outlined in the eMethods. In addition, expert consultations, manual screening of references from relevant studies, and reviews of clinical trial registries were conducted to ensure comprehensive inclusion of applicable studies, including both published and ongoing trials.

## Eligibility Criteria and Screening

The inclusion criteria for this study were as follows: Only RCTs that reported on adult patients (18 years or older) with minor ischemic stroke were eligible. Minor stroke was defined as an NIHSS score of less than 6, irrespective of whether symptoms were classified as disabling. These patients must have been able to receive IVT within 12 hours of symptom onset. The intervention group consisted of patients receiving IVT followed by standard care, while the comparison group received any form of NT-SC or open control including commonly used treatments such as dual antiplatelet therapy, single antiplatelet agents, systemic anticoagulants, statins, antihypertensive medications, blood glucose control therapy, and other interventions aimed at risk factor modification. Exclusion criteria comprised studies that lacked a control group or involved nonrandomized observational designs.

Title, abstract, and full-text screening of articles were conducted and cross-validated against predetermined eligibility criteria, which were independently formulated by 2 reviewers (M.F.D. and N.R.B.). Disagreements were resolved through discussion with the senior author (R.G.N.) when necessary.

## Data Extraction

Data on baseline characteristics, primary end points, secondary end points, and safety end points were systematically extracted from each eligible study by 2 independent investigators to ensure consistency and accuracy. We ensured that no overlapping data were included in the pooled analysis.

Data extraction was conducted from structured reports, which provided comprehensive details including author names, publication year, study design, sample size, types of drugs used for IVT, patient demographic and clinical characteristics, as well as outcome events.

### Outcomes

The primary outcome of this study was an excellent functional outcome at 3 months, defined as mRS score of 0–1. Secondary outcomes included a favorable functional outcome at 90 days (mRS score of 0–2), mortality within 3 months, and recurrent ischemic or hemorrhagic stroke. Safety outcomes encompassed symptomatic intracranial hemorrhage (sICH) and any ICH.

The mRS is an ordinal scale that ranges from 0 to 6, with 0 indicating no disability while death is assigned a score of 6. If a 3-month assessment was available, it was prioritized for analysis; however, in the case of IST-3, we used the 6-month assessment due to the absence of a 3-month evaluation. To ensure consistency across studies, we converted the Oxford Handicap Scale (OHS) outcomes from IST-3 into the corresponding categories of mRS where we mapped the OHS outcome assessment to equivalent mRS categories. Some studies provided multiple definitions for sICH, depending on their criteria including European Cooperative Acute Stroke Study (ECASS) II, ECASS III, National Institute of Neurological Disorders and Stroke (NINDS), the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), and Heidelberg Bleeding Classification.[19-22] For the definition of sICH, we adhered to the primary definition as specified by each study.

### Assessment of Risk of Bias

The Cochrane risk of bias tool (RoB2) was used to assess the quality and potential bias of the included RCTs.[23] This tool is designed to evaluate the risk of bias across 5 key domains: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. For each domain, the risk of bias was rated as low, indicating that the study design and conduct were judged to be unlikely to have introduced systematic error in the results; high, suggesting that there were significant issues in the study that were likely to have introduced systematic error; or raising some concerns, implying that there were potential issues or a lack of information that raised doubts about the results, but not to the extent of a high-risk rating. Two independent reviewers conducted the risk of bias assessment (M.F.D. and N.R.B.), and any discrepancies between reviewers were resolved through discussion, with input from the senior author (R.G.N.) when necessary.

### Statistical Analysis

For each study, effect sizes were calculated as logit-transformed odds ratios (ORs) using random effects and Mantel-Haenszel weighting. The between-study variance in the random-effects models was estimated through restricted maximum likelihood, with 95% CIs. To thoroughly explore the data and mitigate potential bias from heterogeneous definitions and inclusion criteria across studies, we applied various analytical approaches, as presented in eTable 1.[24,25] We conducted multiple sensitivity analyses based on the presence or absence of disabling symptoms, the type of control treatment administered, and the specific thrombolytic agent used. Heterogeneity was evaluated using the $Q$ statistic and $I^2$ test, with $I^2$ values ≥50% or a $p$ value <0.10 from the $Q$ test indicating significant heterogeneity. Publication bias was not assessed due to the small number of included studies (<10), and meta-regression was not performed for the same reason.[17,26,27] In addition, a leave-one-out analysis was conducted by sequentially excluding 1 study at a time to test the robustness of the findings. This comprehensive approach ensured no overlap of data across different pooled analyses and accounted for varying inclusion criteria and scenarios to address the research question while mitigating study-level data heterogeneity. Statistical analyses were performed using Stata software (version 17.0; StataCorp LLC, College Station, TX).

### Data Availability

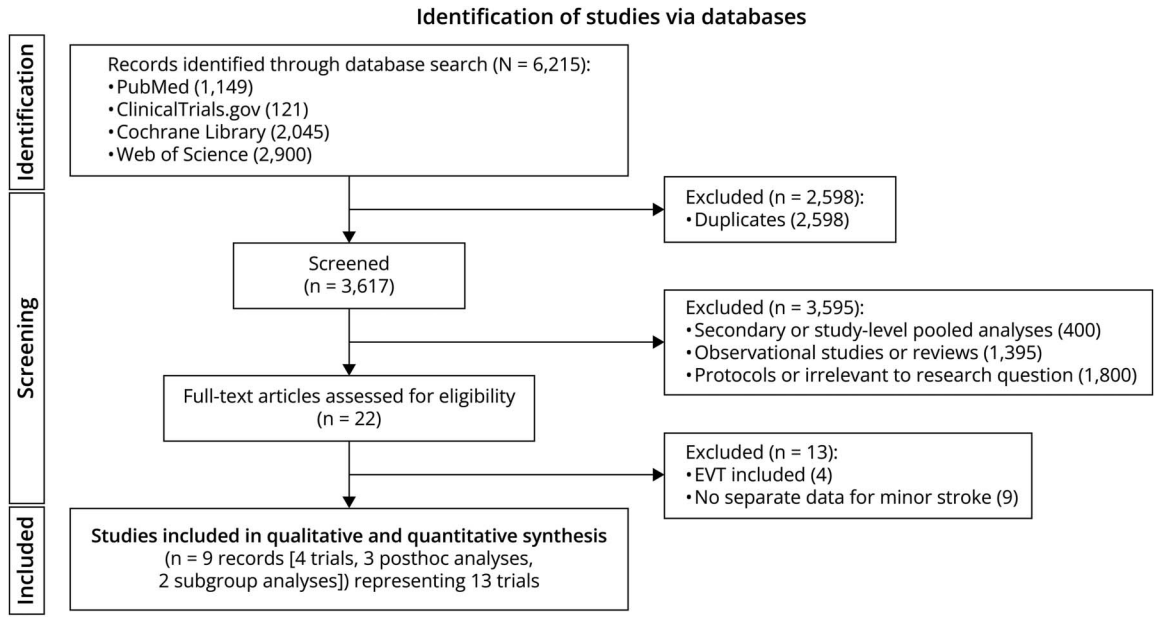
All data generated or analyzed in this study are presented in the main article and Supplementary Materials. The raw data sets (Excel files) used for statistical analyses are available from the corresponding author on reasonable request.

## Results

### Search Results

After a comprehensive search, 6,215 records were identified. After removing duplicates, 3,617 articles were screened based on titles and abstracts. Of these, 22 were considered potentially relevant and underwent full-text review. Ultimately, the analysis included 9 reports representing 13 RCTs (Figure 1). Although the 4 recent RCTs included in our primary analysis focused exclusively on patients with minor strokes (NIHSS <6),[13,14,28,29] the earlier 9 trials included in an IPD meta-analysis by Emberson et al.[9] contributed only a small subset of patients with minor strokes, defined as NIHSS 0–4 in their subgroup analysis. The trials included in the meta-analysis were NINDS A, NINDS B, ECASS I, ECASS II, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A, ATLANTIS B, ECASS III, Effects of Alteplase Beyond 3 Hours After Stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), and IST-3, with a total of 6,756 patients randomized and 666 patients had NIHSS scores <5.[9,19,30-33] Notably, 400 patients (60.1%) in this subgroup were from the IST-3 trial. We identified a post hoc explanatory analysis from the NINDS trials, in which only 58 patients (9.3%) had NIHSS scores ≤5.[34] We also obtained data from a separate post hoc analysis of IST-3 with more restricted inclusion criteria (N = 106), reporting outcomes for mRS 0–1, mRS 0–2, and

**Figure 1** Flow Diagram of the Search Process




EVT = endovascular therapy.

mortality,[35] as well as subgroup data from the main IST-3 publication (N = 612 for NIHSS 0–5) on the mRS 0–2 outcome.[10] A summary table has been added to illustrate the distribution of patients with NIHSS <5 across the 9 trials included in the IPD meta-analysis (eTable 2).

## Study Characteristics

The characteristics of the included studies are summarized in Table 1. These trials involved IVT agents including alteplase, tenecteplase, and pro-urokinase and varied in geographic location, control group, sample size, and inclusion criteria. Although the Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits (PRISMS) and Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke (ARAMIS) RCTs primarily focused on nondisabling symptoms, Prourokinase vs Standard Care for Patients With Mild Ischemic Stroke (PUMICE), Tenecteplase vs Standard of Care for Minor Ischaemic Stroke With Proven Occlusion (TEMPO-2; a randomized, open label, phase 3 superiority trial) along with RCTs included in the Emberson et al. meta-analysis employed broader inclusion criteria.[9,13,14,28,29,36] In the PRISMS trial, nondisabling symptoms were defined as an NIHSS score between 0 and 5, with deficits not deemed clearly disabling at presentation. A deficit was considered "clearly disabling" if, left unchanged, it would prevent the patient from performing basic activities of daily living (such as bathing, ambulating, toileting, hygiene, and eating) or returning to work. This determination was made by local clinicians in consultation with the patient and their family. In the ARAMIS trial, the inclusion criteria required an NIHSS score of 5 or less, with a maximum score of 1 point on single-item assessments such as vision, language, neglect, or unilateral limb weakness and a score of 0 for consciousness at the time of randomization. The PUMICE trial excluded patients with rapidly improving symptoms, and the TEMPO-2 trial needed to have imaging evidence of an intracranial occlusion or indirect evidence with a focal perfusion lesion matching the presenting symptoms. Both the PUMICE and TEMPO-2 trials included subgroup or exploratory analyses focused on patients with disabling strokes. Disabling stroke was defined as the presence of clearly disabling neurologic deficits, consistent with the Re-Examining Acute Eligibility for Thrombolysis (TREAT) Task Force criteria. These deficits included complete or bilateral hemianopia, including cortical blindness (NIHSS item 3 score ≥2); significant weakness in at least 1 arm (NIHSS item 5a or 5b score ≥2) or 1 leg (NIHSS item 6a or 6b score ≥2); severe aphasia or muteness (NIHSS item 9 score ≥2); or profound neglect involving more than 1 sensory modality (NIHSS item 11 score ≥2).[37]

## Risk of Bias Assessment

All the included RCTs were assessed as having a low risk of bias; however, there were concerns regarding data completeness and baseline imbalances in the reported post hoc and subgroup analyses (Table 2).

## Outcomes

### Primary Outcome: Excellent Functional Outcome of mRS Score of 0–1

In the primary analysis, IVT was not significantly associated with higher odds of excellent functional recovery compared

**Table 1** Characteristics of Included Studies

| Study | Khatri 2010 (NINDS rt-PA trials) | Khatri 2015 (IST-3) | Khatri 2018 (PRISMS) | Chen 2023 (ARAMIS) | Coutts 2024 (TEMPO-2) | Xiong 2024 (PUMICE) |
|---|---|---|---|---|---|---|
| **Study design** | Post hoc analysis of RCT | Post hoc analysis of RCT | RCT | RCT | RCT | RCT |
| **No. of sites** | 8 regional centers with 35 affiliated hospitals | 156 | 75 | 38 | 48 | 89 |
| **Enrollment time** | January 1991–October 1994 | May 2000–July 2011 | May 2014–December 2016 | October 2018–April 2022 | April 2015–January 2024 | November 2022–December 2023 |
| **Country** | USA | 12 countries outside the USA: Northwest Europe (the United Kingdom, Austria, Belgium, Switzerland), Australasia, Southern Europe (Italy, Portugal), Scandinavia (Norway, Sweden), Eastern Europe (Poland), Americas (Canada, Mexico) | USA | China | Australia, Canada, Austria, Brazil, Finland, Ireland, New Zealand, Spain, Singapore, and the United Kingdom | China |
| **Pre-mRS** | 4 of minor strokes in rt-PA group had mRS ≥2 | 0–1 | 0–1 | 0–1 | 0–2 | 0–1 |
| **Time window for LKW** | Within 3 h | Within 3 h | Within 3 h | Within 4.5 h | Within 12 h | Within 4.5 h |
| **Disabling status** | Of the 58 cases enrolled, only 2 had isolated aphasia, and 3 had isolated vision loss. No patients were enrolled with isolated motor symptoms, severe limb weakness, facial droop, ataxia, dysarthria, isolated sensory symptoms, or symptoms/signs not captured by the NIHSS score (i.e., NIHSS = 0) | Not specified | Nondisabling | Nondisabling | 100 (11.3%) were identified as having disabling deficits and 786 (88.7%) as having nondisabling deficits | Included both disabling and nondisabling symptoms |
| **Additional inclusion criteria** | NA | Pretreatment blood pressure <185/110, and no other rt-PA exclusion criteria | NA | NA | Evidence of an intracranial occlusion; ASPECTS of 7 or greater | Patients planned to proceed to EVT were excluded |
| **Sample size (control: IVT [n])** | 624 (part 1: 291, part 2: 333)<br>58 with minor stroke (42 rt-PA and 16 placebo) | SOC: 51; IVT: 55 | ASA: 157; IVT: 156 | DAPT: 369; IVT: 350 | BMM: 454; IVT: 432 | BMM: 723; IVT: 723 |
| **Control regimen** | Placebo | In the double-blind phase, both groups were instructed to refrain from antiplatelet or anticoagulant therapy for 24 h. In the open phase, patients in the control group were instructed to begin aspirin treatment immediately | Oral aspirin, 325 mg, with placebo IV alteplase | The DAPT group received a loading dose of 300 mg of clopidogrel on the first day, followed by 75 mg daily for 12 ± 2 days; 100 mg of aspirin on the first day, followed by 100 mg daily for 12 ± 2 days; and continued either single antiplatelet therapy or DAPT according to guidelines for up to 90 d | Nonthrombolytic standard of care (most treated with dual antiplatelet therapy) with aspirin and clopidogrel (259 [57%] of 452) or aspirin monotherapy (106 [23%] of 452) | AP or AC at the discretion of the local investigators (aspirin + clopidogrel [650], aspirin + ticagrelor [10]), patients received DAPT before randomization (9), aspirin (31), clopidogrel (9), ticagrelor (1), direct oral anticoagulant (7), heparin (3), IV prourokinase (3) |
| **IVT drug** | Alteplase | Alteplase | Alteplase | Alteplase | Tenecteplase | Prourokinase |

Continued

**Table 1** Characteristics of Included Studies *(continued)*

| Study | Khatri 2010 (NINDS rt-PA trials) | Khatri 2015 (IST-3) | Khatri 2018 (PRISMS) | Chen 2023 (ARAMIS) | Coutts 2024 (TEMPO-2) | Xiong 2024 (PUMICE) |
|---|---|---|---|---|---|---|
| **Age, y (IVT vs control)** | Mean (SD): 66.2 (12.0) | Median (82; 81) | Mean (SD): 62 (14) vs 61 (13) | 64 (56–71) vs 65 (57–71) | 72 (62–80); 72 (61–79) | 65.9 (57.6–73.2); 65.9 (58.0–72.2) |
| **Male sex, n (%)** | 42 (72.4) | 56.4; 62.7 | 77 (49) vs 92 (59) | 240 (68.6); 256 (69.5) | 244 (65); 272 (60%) | 479 (66.3); 469 (64.9) |
| **Onset to treatment time** | NA | 2.5 h for both groups | 2.7 (2.2–2.9) vs 2.8 (2.4–3.1) | 180 (126–225); 182 (134–230) | 293 (165–453); 311 (184–495) | 187.0 (142.0–225.0); 184.0 (138.0–223.0) |
| **Baseline NIHSS score** | Median and range: 4 (4) | Median 4 for both | 2.3 (1.2) vs 2.0 (1.2) | 2 (1–3) for both | 2 (1–3) for both | 3 (2–4); 2 (1–3) |
| **Baseline ASPECTS** | NA | NA | 10 (7–10) for both | NA | 10 (9–10) for both | 10 (9–10) for both |

Abbreviations: ASA = aspirin; ASPECTS = Alberta Stroke Program Early CT Score; BMM = best medical management; DAPT = dual antiplatelet therapy; EVT = endovascular therapy; IVT = IV thrombolysis; LKW = last known well; NA = not applicable/available; NIHSS = NIH Stroke Scale; pre-mRS = pre–stroke modified Rankin Scale; RCT = randomized controlled trial; rt-PA = alteplase; SOC = standard of care.

with NT-SC (mRS 0–1; OR 0.85, 95% CI 0.70–1.03). Subgroup analyses by IVT type also showed no significant benefit with alteplase (OR 0.76, 95% CI 0.51–1.13), prourokinase (OR 0.76, 95% CI 0.54–1.07), or tenecteplase (OR 0.97, 95% CI 0.73–1.30; Figure 2A). Similarly, outcomes were consistent across control regimens, including aspirin alone, dual antiplatelet therapy (DAPT), and other standard care approaches (eFigure 1A). Sensitivity analyses, including leave-one-out tests, supported the robustness of these findings, with no single trial significantly influencing the pooled estimates or heterogeneity (eFigure 2A). Adding data from a meta-analysis subgroup (NIHSS 0–4) across 9 trials or post hoc analyses of IST-3 and NINDS trials provided evidence of consistent findings (Figure 2B, eFigure 1B). Notably, subgroup analysis symptoms showed a nonsignificant association of IVT with odds of excellent functional recovery across both groups with disabling symptoms (OR 0.84, 95% CI 0.38–1.88) and nondisabling symptoms (OR 0.82, 95% CI 0.66–1.03) (Figure 2C). In addition, including data from a meta-analysis subgroup (NIHSS 0–4) across 9 trials or post hoc analyses of IST-3 and NINDS trials to the disabling subgroup did not alter the findings (eFigure 1, C and D).

### Independent Functional Outcome of mRS Score of 0–2

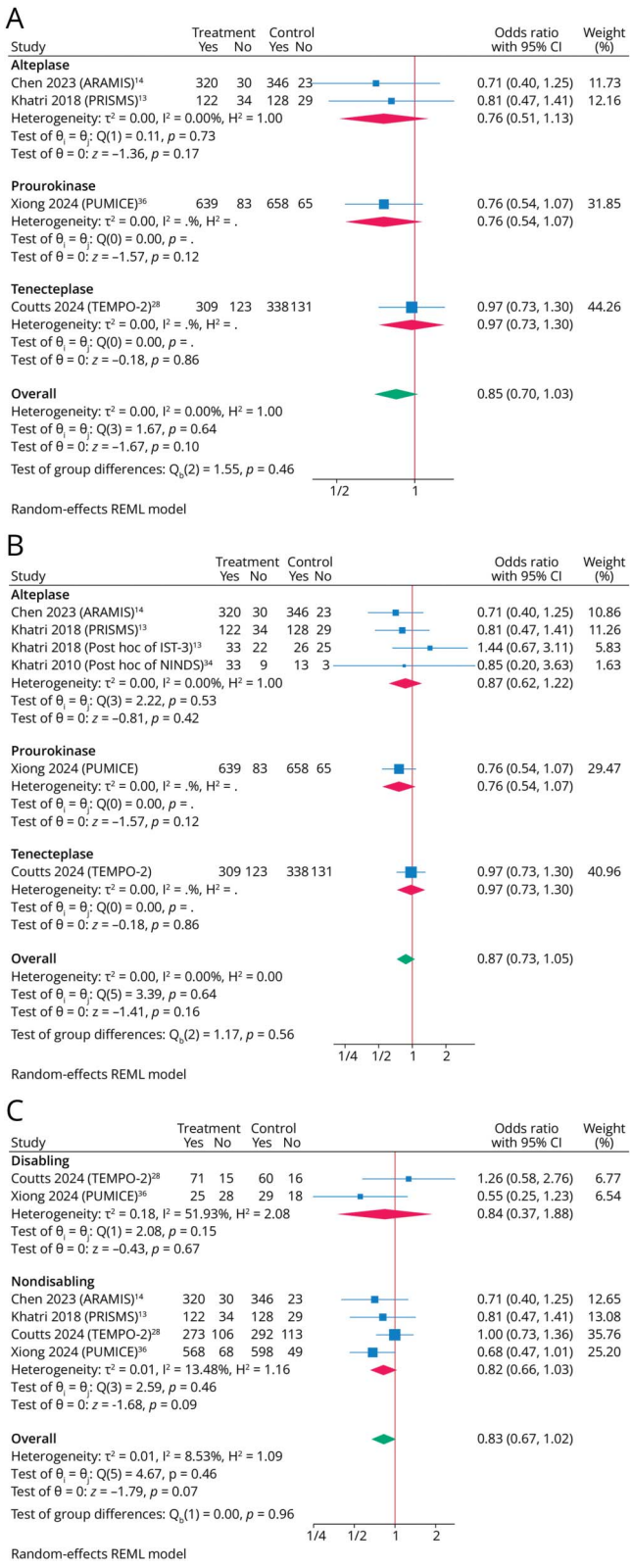
In the primary analysis, IVT was significantly associated with lower odds of achieving an independent functional outcome (mRS 0–2 at 90 days) compared with NT-SC (OR 0.71, 95% CI 0.55–0.91; eFigure 3A). Sensitivity analyses, including leave-one-out tests, confirmed the robustness of this finding, with no single trial unduly influencing the pooled effect or heterogeneity (eFigure 2B). When incorporating post hoc data from IST-3, the association was no longer significant (OR 0.85, 95% CI 0.58–1.24; eFigure 3B). However, when the IST-3 subgroup data with broader criteria were added to the pooled analysis, IVT remained significantly associated with lower odds of achieving an independent outcome (eFigure 3C).

**Table 2** Results of Risk of Bias Assessment Using the Cochrane Collaboration's Tool

| Study | Randomization process | Deviation from the intended intervention | Missing outcomes | Measurement of the outcome | Selection of the reported results | Overall |
|---|---|---|---|---|---|---|
| **Khatri 2015 (IST-3)** | + | + | + | + | ?[a] | ? |
| **Khatri 2018 (PRISMS)** | + | + | + | + | + | + |
| **Chen 2023 (ARAMIS)** | + | + | + | + | + | + |
| **Coutts 2024 (TEMPO-2)** | + | + | + | + | + | + |
| **Xiaong 2024 (PUMICE)** | + | + | + | + | + | + |
| **Khatri 2010 (NINDS trials)** | + | + | + | + | ?[a] | ? |

+ = low risk of bias; ? = some concerns; − = high risk of bias.
[a] Unclear if all available outcomes were reported.

**Figure 2** Excellent Functional Outcome (mRS 0–1 at 90 Days)




(A) Subgroup analysis by IVT type and overall results from 4 RCTs. (B) Subgroup analysis by IVT type, incorporating overall results from the 4 RCTs and post hoc data from IST-3 and NINDS trials. (C) Subgroup analysis by disabling vs nondisabling symptoms from 4 RCTs. IST-3 = third International Stroke Trial; IVT = IV thrombolysis; mRS = modified Rankin Scale; RCT = randomized controlled trial.

### Ninety-Day Mortality

At 90 days, IVT was associated with a significantly higher risk of mortality compared with NT-SC (OR 2.40, 95% CI 1.23–4.67; Figure 3A). Sensitivity analyses, including leave-one-out tests, confirmed the robustness of this finding, with no single trial unduly affecting the pooled effect or heterogeneity (eFigure 2C). However, when post hoc data from IST-3 and NINDS were included in the pooled analysis, the difference in mortality between treatment groups was no longer significant (Figure 3B).

### Hemorrhagic Transformation

The overall pooled estimate showed that IVT was associated with a significantly higher odds of sICH compared with NT-SC (OR 5.22, 95% CI 1.76–15.48; Figure 4A). Subgroup analysis based on sICH definition revealed variability in sICH rates across different groups (Figure 4B). Sensitivity analyses, including leave-one-out tests, confirmed the robustness of the results, with no trial disproportionately affecting the pooled effect or heterogeneity (eFigure 2D). Incorporating post hoc data from NINDS trials supported these consistent findings (Figure 4C). IVT was associated with significantly higher odds of ICH (OR 1.72, 95% CI 1.17–2.54; eFigure 4). Sensitivity analyses, including leave-one-out tests, confirmed the robustness of the results, with no single trial disproportionately affecting the pooled effect size or heterogeneity (eFigure 2E).

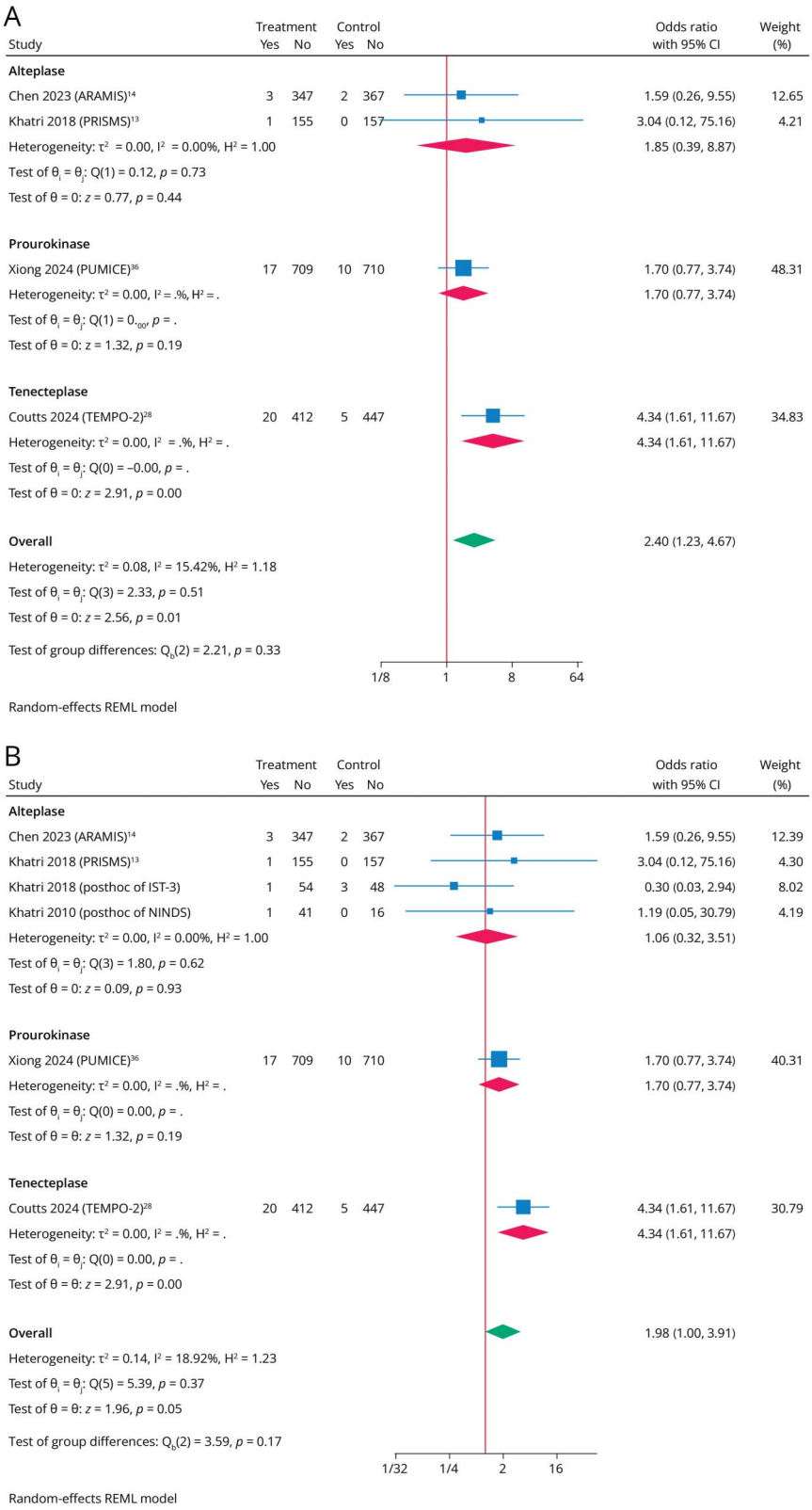
### Recurrent Stroke

No significant difference in recurrent stroke was observed between treatment groups (OR 1.08, 95% CI 0.60–1.97; eFigure 5). Sensitivity analyses, including leave-one-out tests, confirmed the robustness of the results, with no single trial disproportionately affecting the pooled effect size or heterogeneity (eFigure 2F).

## Discussion

This meta-analysis, comparing IVT with NT-SC for minor AIS, primarily based on 4 RCTs focusing predominantly on nondisabling minor strokes, found that IVT did not improve functional outcomes. IVT was not associated with better rates of excellent functional recovery (mRS 0–1) but was linked to a lower rate of functional independence (mRS 0–2) at 90 days compared with NT-SC. In addition, IVT was associated with higher odds of sICH and increased mortality within 90 days. These results were further supported by secondary and subgroup analyses. This elevated sICH risk with IVT without any counterbalancing benefit is a significant concern. This suggests that the potential reperfusion benefits of IVT in minor AIS may be outweighed by the increased risk of hemorrhagic complications. Furthermore, the observed increased mortality in IVT-treated patients underscores the potential trade-off between modest functional recovery and heightened risks. Our consistent subgroup and sensitivity analysis supports the notion that the

**Figure 3** Mortality Within 90 Days

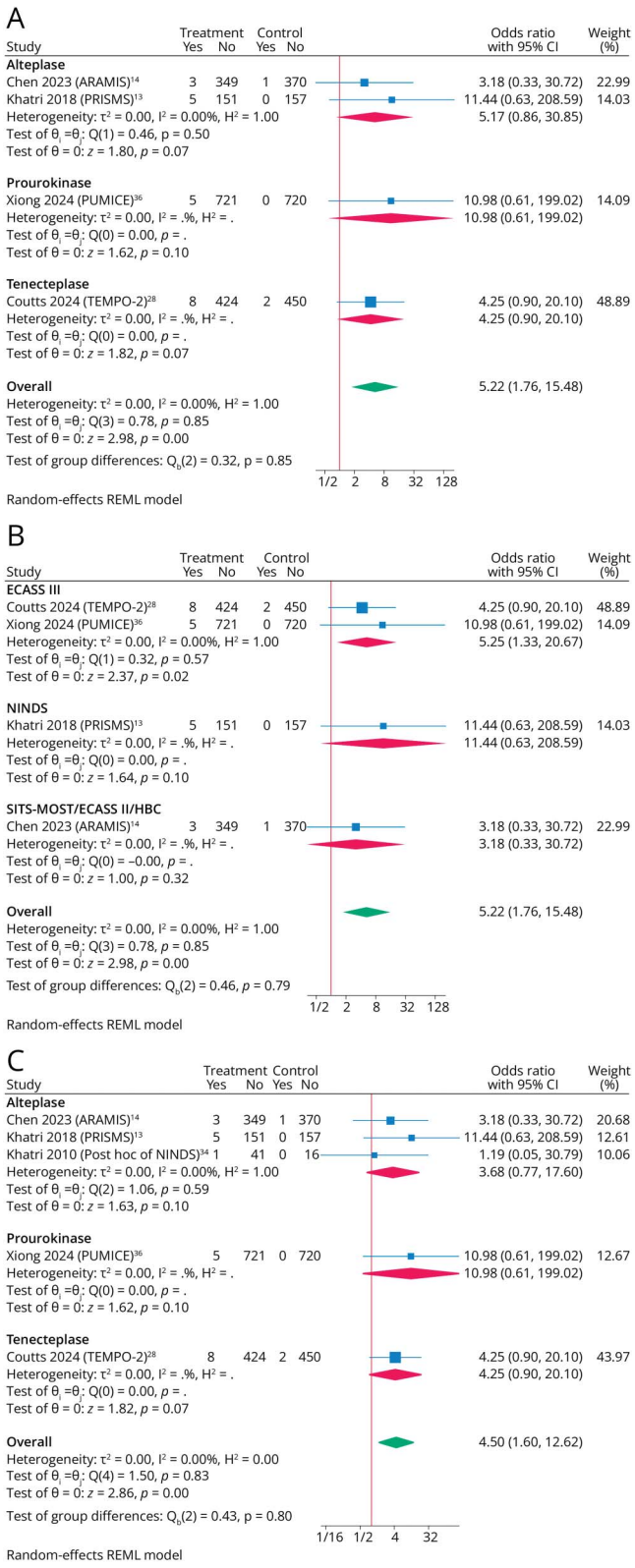



(A) Subgroup analysis by IVT type and overall results from 4 RCTs. (B) Expanded analysis including IST-3 post hoc and NINDS data, providing a comprehensive view of the impact of IVT types on mortality. IST-3 = third International Stroke Trial; IVT = IV thrombolysis; RCT = randomized controlled trial.

lack of efficacy of IVT in minor AIS is not specific to the thrombolytic agent used but rather reflects the overall risk-benefit profile of IVT for this group of patients.

Although the PRISMS and ARAMIS RCTs primarily focused on patients presenting with nondisabling stroke symptoms, the PUMICE and TEMPO-2 trials—as well as the RCTs

**Figure 4** Symptomatic Intracranial Hemorrhage




(A) Subgroup analysis by IVT type and overall results from 4 RCTs. (B) Subgroup analysis based on the definition of sICH used in the trials, with overall results from the 4 RCTs. (C) Analysis including NINDS post hoc data. IVT = IV thrombolysis; RCT = randomized controlled trial; sICH = symptomatic intracranial hemorrhage.

included in the Emberson et al. meta-analysis—adopted broader inclusion criteria, enrolling patients with a wider range of symptom severity.[9,13,14,28,36] An exploratory secondary analysis of the TEMPO-2 trial that aimed to determine if the presence of disabling deficits modified this treatment effect. Among the 886 patients in the TEMPO-2 trial, 100 (11.3%) were identified as having disabling deficits and 786 (88.7%) as having nondisabling deficits. Although there was no evidence of treatment effect heterogeneity between the groups ($p$-interaction = 0.22), nominally fewer excellent outcomes at 90 days (mRS 0–1) were observed with tenecteplase in the disabling group (47.2% vs 61.7%, $p = 0.164$) compared with standard of care, while no such difference was noted in the nondisabling group (72.0% vs 72.5%, $p = 0.936$). No difference was found in sICH rates; however, a significant interaction existed between the treatment arm and the presence of disabling stroke regarding any hemorrhage on follow-up neuroimaging (tenecteplase 20.8% vs control 2.1%, $p = 0.005$ in the disabling group; tenecteplase 13.5% vs control 10.0%, $p = 0.146$ in the nondisabling group; $p$-interaction = 0.049). It should be noted that the observed numerically lower rates of excellent outcomes in the disabling deficits group receiving tenecteplase may be attributable to their longer times to presentation and thrombolysis compared with the control group (288 minutes vs 133 minutes, $p < 0.001$).[38] Similar findings regarding the lack of benefit of non-IVT treatment in improving rates of excellent functional recovery were recently confirmed in a small subgroup analysis from the PUMICE trial and further supported by our pooled analysis of both trials.[29] These findings, along with our pooled results, also put into question the current American Heart Association and European Stroke Organization guidelines, which recommend IVT for minor strokes with disabling deficits.[7,8] As the level of evidence for IVT in mild disabling strokes is limited, our data provide new insights that could refine these guidelines. Specifically, IVT does not offer significant benefits for nondisabling strokes but may expose patients to additional risks. This evidence, supported by the recent RCTs we included,[28,29,36,39] has the potential to alter the level of evidence in future guidelines. In addition, data from the NINDS trials demonstrated that the odds of achieving a good outcome (mRS of 0 at 3 months) were not significant for patients with an NIHSS score of 1–7 (OR 1.41, 95% CI 0.65–3.08). This suggests that the benefits of alteplase were primarily driven by moderate strokes, even when NIHSS scores of 6 and 7 were included in the minor AIS subgroup.[40] The difference was even less pronounced when using mRS 0–1 as the outcome (76.4% vs 69.8% for rt-PA and placebo, respectively).[40] A study based on the NINDS trials applied 5 definitions of minor stroke (using NIHSS and clinical data) and reported treatment benefits. However, these findings were based on post hoc analyses that included patients with NIHSS scores as high as 11.[41] Moreover, among patients with NIHSS scores of 0–5, 72% were assigned to the alteplase group compared with 28% in the placebo group, revealing a significant imbalance in the 91-minute to 180-minute treatment window (19% of

alteplase-treated patients had NIHSS <5 vs 4% in the placebo group).[41-43] Among the 624 patients enrolled in the NINDS trials, only 58 (9.3%) had NIHSS scores ≤5. As previously reported by the NINDS investigators, patients with isolated ataxia, dysarthria, facial weakness, sensory symptoms, or isolated symptoms not captured by the NIHSS (i.e., NIHSS = 0) were explicitly excluded. Furthermore, for the isolated deficits not listed as explicit exclusions, only 3 or fewer patients were enrolled per deficit. In this underpowered subgroup from NINDS trials (β <25%), minimal or no disability (mRS 0–1) was observed in 33 of 42 rt-PA–treated patients (78.6%, 95% CI 63.2%–89.7%) and 13 of 16 placebo-treated patients (81.3%, 95% CI 54.4%–96.0%). No significant treatment effect was observed (OR 0.85, 95% CI 0.20–3.63).[34] Furthermore, the current guideline recommendation of IVT in minor strokes with disabling deficits is largely derived from an exploratory subgroup analysis of a meta-analysis of 9 RCTs, involving 666 patients (10%) with baseline NIHSS scores of 0–4. Although no significant difference in alteplase efficacy was noted across mild, moderate, and severe strokes, a notable trend was observed ($p$-interaction = 0.06). Similarly, IST-3 demonstrated a smaller benefit of IVT in minor strokes, with 72.7% of the r-tPA group and 75.3% of the control group achieving an OHS of 0–2 at 6 months (OR for NIHSS 0–5: 0.85, 95% CI 0.52–1.38).[9] An analysis of the GWTG-Stroke registry demonstrated that, among 5,910 patients who presented with NIHSS ≤5 (median 4 [interquartile range 3–5]) and received IV alteplase within 4.5 hours from stroke onset, 30.3% could not ambulate independently at discharge.[6] Moreover, MaRISS was another prospective observational study of 1,765 patients (age 65 ± 14; 42% women) with NIHSS ≤5 within 4.5 hours of symptom onset, across 100 GWTG-Stroke hospitals. Symptoms resolved completely in 10% (TIA), while 90% had persistent deficits (AIS). Alteplase-treated patients were younger, had fewer comorbidities, were more often treated at high-volume teaching hospitals, and had higher NIHSS scores (2.9 ± 1.4 vs 1.7 ± 1.4). After adjusting for confounders, alteplase showed no effect on the primary outcome (90-day mRS 0–1) or secondary outcomes. A modest, unadjusted association with Stroke Impact Scale-16 was seen in patients with NIHSS 3–5.[11] An analysis of data from a prospective stroke unit registry for mild noncardioembolic stroke (NIHSS 0–3) further supports these findings. Despite IVT leading to increased occurrences of sICH and early neurologic deteriorations, no significant difference in functional outcomes between the IVT and DAPT treatment groups was obtained.[44]

Although evidence strongly suggests that NT-SC may be a safer and equally effective alternative to IVT in patients with minor AIS, the different subgroups of controls in our study showed similar results compared with endovascular therapy (EVT). The Clopidogrel Plus Aspirin vs Aspirin Alone in Patients With Acute Mild to Moderate Stroke (ATAMIS) trial, which evaluated the efficacy of DAPT (clopidogrel plus aspirin) vs aspirin alone in patients with acute mild to moderate ischemic stroke, enrolled 3,000 patients within 48 hours of symptom onset. The results showed that dual antiplatelet therapy significantly reduced early neurologic deterioration (4.8% vs 6.7%) compared with aspirin alone (risk difference −1.9%, 95% CI −3.6 to −0.2; $p = 0.03$), with similar bleeding rates between the 2 groups.[39] In addition, a network meta-analysis of 5 major trials (CHANCE, POINT, PRINCE, THALES, and CHANCE-2) involving over 28,000 patients found that DAPT with aspirin and ticagrelor was more effective than aspirin alone in preventing recurrent ischemic stroke, without increasing the risk of hemorrhagic stroke or death.[45] Ongoing trials, including the ENDOLOW trial (NCT04167527) within the STEP Platform (NCT06289985) and the MOSTE trial (NCT03796468), are evaluating the efficacy of EVT in minor AIS and large vessel occlusion, which may refine treatment strategies for this patient population.

While this meta-analysis offers valuable insights, several limitations must be acknowledged. The inclusion of post hoc analyses and aggregate data from subgroup studies introduces the potential for bias, although sensitivity and secondary analyses were performed to mitigate this issue. In addition, variations in disabling symptom definition, treatment protocols, and follow-up duration across studies limit the generalizability of the results. To address these gaps, further high-quality RCTs focused specifically on minor AIS with disabling deficits are necessary. Future guidelines may benefit from incorporating risk stratification tools that integrate clinical, imaging, and biomarker data, allowing for better identification of patients who may derive net benefit from IVT. Advanced imaging techniques, such as perfusion imaging, could play a key role in identifying "at-risk" penumbral tissue in minor strokes, facilitating more tailored and precise treatment decisions.

In conclusion, our meta-analysis provides evidence that IVT does not offer substantial benefit in patients with minor AIS and is associated with increased risks of sICH and mortality. These findings support a cautious approach to IVT in minor AIS, emphasizing the importance of individualized risk assessment in treatment decisions. For patients with minor AIS without disabling deficits, NT-SC, including DAPT or anticoagulation (if appropriate), is a safer and likely more effective treatment strategy. Since most of the included patients seem to be presenting with nondisabling minor strokes, additional studies considering patients with mildly disabling symptoms are warranted.

## Author Contributions

M.F. Doheim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. T.N. Nguyen: drafting/revision of the manuscript for content, including medical writing for content. Y. Xiong: drafting/revision of the manuscript for content,

including medical writing for content. H.-S. Chen: drafting/revision of the manuscript for content, including medical writing for content. N.R. Bhatt: drafting/revision of the manuscript for content, including medical writing for content. Y. Wang: drafting/revision of the manuscript for content, including medical writing for content. R.G. Nogueira: drafting/revision of the manuscript for content, including medical writing for content.


## Study Funding

No targeted funding reported.


## Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.


## Publication History

Received by *Neurology*® January 17, 2025. Accepted in final form April 30, 2025. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.


## References


1. Steinmetz JD, Seeher KM, Schiess N, et al. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease study 2021. *Lancet Neurol*. 2024;23(4):344-381. doi:10.1016/S1474-4422(24)00038-3
2. Reeves M, Khoury J, Alwell K, et al. Distribution of National Institutes of Health Stroke scale in the Cincinnati/Northern Kentucky Stroke Study. *Stroke*. 2013;44(11):3211-3213. doi:10.1161/STROKEAHA.113.002881
3. Saber H, Khatibi K, Szeder V, et al. Reperfusion therapy frequency and outcomes in mild ischemic stroke in the United States. *Stroke*. 2020;51(11):3241-3249. doi:10.1161/STROKEAHA.120.030898
4. Smith EE, Fonarow GC, Reeves MJ, et al. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: findings from Get With The Guidelines-Stroke. *Stroke*. 2011;42(11):3110-3115. doi:10.1161/STROKEAHA.111.613208
5. Khatri P, Conaway MR, Johnston KC; Acute Stroke Accurate Prediction Study ASAP Investigators. Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke*. 2012;43(2):560-562. doi:10.1161/STROKEAHA.110.593897
6. Romano JG, Smith EE, Liang L, et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With The Guidelines-Stroke Registry. *JAMA Neurol*. 2015;72(4):423-431. doi:10.1001/jamaneurol.2014.4354
7. Powers WJ, Rabinstein AA, Ackerson T, 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(12):e344-e418. doi:10.1161/STR.0000000000000211
8. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6(1):I-LXII. doi:10.1177/2396987321989865
9. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384(9958):1929-1935. doi:10.1016/S0140-6736(14)60584-5
10. 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(9834):2352-2363. doi:10.1016/S0140-6736(12)60768-5
11. Romano JG, Gardener H, Campo-Bustillo I, et al. Predictors of outcomes in patients with mild ischemic stroke symptoms: MaRISS. *Stroke*. 2021;52(6):1995-2004. doi:10.1161/STROKEAHA.120.032809
12. Zhang Y, Lv T, Nguyen TN, et al. Intravenous alteplase versus best medical therapy for patients with minor stroke: a systematic review and meta-analysis. *Stroke*. 2024;55(4):883-892. doi:10.1161/STROKEAHA.123.045495
13. Khatri P, Kleindorfer DO, Devlin T, et al. 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(2):156-166. doi:10.1001/jama.2018.8496
14. Chen HS, Cui Y, Zhou ZH, et al. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA*. 2023;329(24):2135-2144. doi:10.1001/jama.2023.7827
15. Qin M, Liu T, Shi X, et al. Antiplatelet therapy versus intravenous thrombolysis for mild acute ischaemic stroke: a living systematic review and meta-analysis. *Stroke Vasc Neurol*. 2025;10(2):e003097. doi:10.1136/svn-2024-003097
16. Alhazzani A, Al-Ajlan FS, Alkhiri A, et al. Intravenous alteplase in minor nondisabling ischemic stroke: a systematic review and meta-analysis. *Eur Stroke J*. 2024;9(3):521-529. doi:10.1177/23969873241237312
17. Chandler J, Cumpston M, Li T, Page MJ, Welch V. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley; 2019.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
19. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352(9136):1245-1251. doi:10.1016/s0140-6736(98)08020-9
20. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329. doi:10.1056/NEJMoa0804656
21. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369(9558):275-282. doi:10.1016/S0140-6736(07)60149-4
22. Neuberger U, Möhlenbruch MA, Herweh C, Ulfert C, Bendszus M, Pfaff J. Classification of bleeding events: comparison of ECASS III (European Cooperative Acute Stroke Study) and the New Heidelberg Bleeding Classification. *Stroke*. 2017;48(7):1983-1985. doi:10.1161/STROKEAHA.117.016735
23. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev*. 2019;10(10):ED000142. doi:10.1002/14651858.ED000142
24. Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. *Res Synth Methods*. 2010;1:2-19. doi:10.1002/jrsm.4
25. Sutton AJ, Kendrick D, Coupland CA. Meta-analysis of individual- and aggregate-level data. *Stat Med*. 2008;27(5):651-669. doi:10.1002/sim.2916
26. Sutton AJ, Duval SJ, Tweedie R, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ*. 2000;320(7249):1574-1577. doi:10.1136/bmj.320.7249.1574
27. Smid GE, Mooren TT, van der Mast RC, Gersons BP, Kleber RJ. Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies. *J Clin Psychiatry*. 2009;70(11):1572-1582. doi:10.4088/JCP.08r04484
28. Coutts SB, Ankolekar S, Appireddy R, et al. 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(10444):2597-2605. doi:10.1016/S0140-6736(24)00921-8
29. Xiong Y, Meng X, Jin A, et al. Prourokinase vs standard care for patients with mild ischemic stroke: the pumice randomized clinical trial. *JAMA Neurol*. 2025;82(3):258-266. doi:10.1001/jamaneurol.2024.4688
30. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1588. doi:10.1056/NEJM199512143332401
31. Boysen G; ECASS Study Group. European Cooperative Acute Stroke Study (ECASS):(rt-PA—Thrombolysis in acute stroke) study design and progress report. *Eur J Neurol*. 1995;1(3):213-219. doi:10.1111/j.1468-1331.1995.tb00074.x
32. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA*. 1999;282(21):2019-2026. doi:10.1001/jama.282.21.2019
33. Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7(4):299-309. doi:10.1016/S1474-4422(08)70044-9
34. Khatri P, Kleindorfer DO, Yeatts SD, et al. Strokes with minor symptoms: an exploratory analysis of the NINDS rt-PA trials. *Stroke*. 2010;41(11):2581-2586. doi:10.1161/strokeaha.110.593632
35. Khatri P, Tayama D, Cohen G, et al. Effect of intravenous recombinant tissue-type plasminogen activator in patients with mild stroke in the third International Stroke Trial-3: post hoc analysis. *Stroke*. 2015;46(8):2325-2327. doi:10.1161/STROKEAHA.115.009951
36. Xiong Y, Hao M, Pan Y, et al. Rationale and design of ProUrokinase in Mild IsChemic strokE (PUMICE): a multicentre, prospective, randomised, open-label, blinded-endpoint controlled trial. *Stroke Vasc Neurol*. 2024;9(6):715-722. doi:10.1136/svn-2023-002673
37. Levine SR, Khatri P, Broderick JP, et al. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: part 1: rapidly improving stroke symptoms. *Stroke*. 2013;44(9):2500-2505. doi:10.1161/STROKEAHA.113.000878
38. Zhang Y, Buck B, Catanese L, et al. Abstract 4: thrombolysis with tenecteplase in minor disabling versus non-disabling stroke: secondary analysis of the TEMPO-2 trial. *Stroke*. 2025;56(suppl 1):A4. doi:10.1161/str.56.suppl_1.4
39. Chen H-S, Cui Y, Wang X-H, et al. Clopidogrel plus aspirin vs aspirin alone in patients with acute mild to moderate stroke: the ATAMIS randomized clinical trial. *JAMA Neurol*. 2024;81(5):450-460. doi:10.1001/jamaneurol.2024.0146

40. Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. *Stroke*. 2007;38(2):414-416. doi:10.1161/01.STR.0000254580.39297.3c
41. National Institute of Neurological Disorders Stroke rt-PA Stroke Study Group. Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience. *Ann Emerg Med*. 2005;46(3):243-252. doi:10.1016/j.annemergmed.2005.02.013
42. Ingall TJ, O'Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke*. 2004;35(10):2418-2424. doi:10.1161/01.STR.0000140891.70547.56
43. Kwiatkowski T, Libman R, Tilley BC, et al. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. *Ann Emerg Med*. 2005;45(4):377-384. doi:10.1016/j.annemergmed.2004.06.021
44. Sykora M, Krebs S, Miksova D, et al. IV thrombolysis vs early dual antiplatelet therapy in patients with mild noncardioembolic ischemic stroke. *Neurology*. 2023;101(9):e933-e939. doi:10.1212/WNL.0000000000207538
45. Lim A, Ma H, Ly J, et al. Comparison of dual antiplatelet therapies for minor, nondisabling, acute ischemic stroke: a Bayesian network meta-analysis. *JAMA Netw Open*. 2024;7(5):e2411735. doi:10.1001/jamanetworkopen.2024.11735