Medical management versus intravenous thrombolysis for patients with minor non-disabling acute ischemic stroke: A systematic review and meta-analysis

*[1]Zhuyan An *MS*, *[2]Qi Wei *MS*, [3]Fang Xie *MS*, [3]Hai Hu *MS*, [3]Guohui Ye *MS*, [1]Qi Li *MS*, [4]Yuqi Peng *MS*, [5]Guangui Yang *MS*

*ZY An and Q Wei contribute equally to this work and are co-first author

[1]Department of Neurology, No. 903 Hospital of PLA Joint Logistic Support Force, Hangzhou, China; [2]Department of Neurology, Shuangliu District Traditional Chinese Medical Hospital, Chengdu, China; [3]Department of Neurology, Xingguo People's Hospital, Xinguo Hospital of Gannan Medical University, Xingguo County, China; [4]Department of Neurology, Sichuan Science City Hospital, Mianyang, China; [5]Department of Neurosurgery, Xingguo People's Hospital, Xinguo Hospital of Gannan Medical University, Xingguo Country, China

Abstract

Background: The efficacy and safety of thrombolysis therapy in patients with mild stroke, especially acute non-disabling stroke is controversial. We intend to conduct this systematic review and meta-analysis to evaluate the efficacy and safety of thrombolytic therapy compared to medical management in acute non-disabling stroke. *Methods:* We searched multiple databases to obtain articles related to medical management and intravenous thrombolysis therapy for minor non-disabling acute ischemic stroke from inception until November 28, 2023, and the search was conducted again on September 1, 2024. The primary outcome was functional independence (modified Rankin scale [mRS] score of 0 to 2) at 90 days. All analyses were performed using the random effect model. The quality of articles was evaluated through the Cochrane risk assessment tool and Newcastle-Ottawa scale. *Results:* 2 RCTs and 7 cohort studies met the inclusion criteria. The merge analysis showed that there was no significant difference in improving functional independence (mRS 0-2, RR: 1.01, 95% CI 0.98 - 1.04, P = 0.47) and excellent outcome (mRS 0-1) of patients with minor non-disabling acute ischemic stroke between IVT and medical management. However, IVT would increase the risk of early neurological deterioration (RR: 0.50, 95% CI 0.30 - 0.82, P = 0.007), compared to medical management. Analysis of the cohort studies showed that there was a significant correlation between IVT and sICH (RR: 0.20, 95% CI: 0.06 - 0.68, P=0.01).
Conclusions: For patients with minor non-disabling acute ischemic stroke, medical management will not have a negative impact on functional recovery, and may be a safer alternative.

Keywords: Non-disabling, acute ischemic stroke, meta-analysis

INTRODUCTION

Acute ischemic mild stroke is usually defined as National Institutes of Health Stroke Scale (NIHSS) score less than or equal to 3 or 5[1-7], accounting for approximately 50% of ischemic stroke.[8,9] Intravenous thrombolysis is an effective treatment to acute ischemic stroke, but whether intravenous thrombolysis can be used for mild stroke patients, especially those without disability, is still controversial. Several observational studies have explored this issue, but achieved conflicting results.[10-17] A Canada study showed that one-third of patients with mild stroke who did not receive thrombolytic therapy were left either dependent or dead.[18] Acute Ischemic Stroke and Minor Non-disabling Neurologic Deficits (PRISMS) study further compared the safety and effectiveness of alteplase and aspirin in patients with mild non-disabling stroke. The results showed that there was no significant difference in 90-day functional outcome between the two

Address correspondence to: Guangui Yang, MS, Department of Neurosurgery, Xingguo People's Hospital, Xinguo Hospital of Gannan Medical University, No. 699, Wenming Avenue, Xingguo County 342400, China. E-mail: yangguanguichn@163.com; Yuqi Peng, MS, Department of Neurology, Sichuan Science City Hospital, 64, Mianshan Road, Youxian District, Mianyang 621000, China. E-mail: pyq31858@163.com

Date of Submission: 19 August 2024; Date of Acceptance: 28 August 2024

https://doi.org/10.54029/2024rkh

groups, but the incidence of symptomatic cerebral hemorrhage(sICH) in alteplase group was higher.[19] The American Heart Association/American Stroke Association Guidelines for Early Management of Acute Ischemic Stroke (updated in 2019) and the European Stroke Organization Guidelines for Intravenous Thrombolysis of Acute Ischemic Stroke (updated in 2021) both recommend that patients with acute disabling mild stroke should be treated with intravenous alteplase within the onset time window of 4.5 h, but thrombolysis is not recommended for patients with acute non-disabling mild stroke.[20,21]

The efficacy and safety of thrombolysis therapy in patients with mild stroke, especially acute non-disabling stroke is controversial. With the deepening of research and the publication of the results of Antiplatelet vs R-tPA for Acute Mild Ischemic Stoke (ARAMIS) trail, a multicenter, randomized controlled trial[19], we intend to conduct this systematic review and meta-analysis to evaluate the efficacy and safety of intravenous thrombolysis (IVT) compared to standard medical management (MM) in acute non-disabling stroke.

METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[22] This study protocol was registered on the International Prospective Register of Systematic Reviews on January 20, 2024 (PROSPERO, CRD42024503351). Data are available on request to the corresponding authors.

Data source and search strategy

We searched the PubMed, Embase, Cochrane Library, Scopus and Web of Science databases to obtain articles in all languages from inception until November 28, 2023. "Stroke","Thrombolytic Therapy" and "Non disabling" were the search terms. Synonyms were obtained from PubMed, Embase and Cochrane Library with elimination of duplicates. Detailed search criteria of keywords and their synonyms are provided in Table S1. The search was conducted again on September 1, 2024.

Eligibility criteria

The inclusion criteria for this acute non-disabling stroke systematic review and meta-analysis were as follows: (1) patients diagnosed with acute ischemic stroke and treated within 4.5 hours; (2) NIHSS score was ≤ 5 and each single item score was ≤ 1 or the article indicated that the included patients were mild non-disabling stroke; (3) interventional arm receiving intravenous thrombolysis (IVT); (4) control arm receiving standard medical management and (5) reporting of mRS score at 3 months, 90-day mortality, and sICH. Studies were excluded if it lacked report of the primary study outcomes or if it lacked reporting of a control group.

Study selection and data collection

The titles, abstracts, and full texts of the articles were read by two researchers working independently (ZY A, QW), selected according to the inclusion and exclusion criteria from a pre-designed table as detailed in Table S2. The two researchers conducted cross-checking after screening of the articles, and if there was disagreement, it was resolved through discussion with the senior author (GG Y). Data of the baseline characteristics, primary, secondary, and safety endpoints of each study were extracted for analysis by two researchers independently (QL, QW).

Risk of bias assessment and quality of evidence

The quality of the RCTs and risk of bias was evaluated with the Cochrane risk assessment tool. The cohort and case-control studies were evaluated by the Newcastle-Ottawa Scale (NOS). For retrospective studies, an evaluation result ≥ 5 ☆ was considered of good quality and was included in the meta-analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of evidence. Publication bias was examined by Egger's test.

Effect measures

The primary outcome was functional independence (defined as a modified Rankin scale [mRS] score of 0 to 2) at 90 days. The secondary outcomes were excellent outcome (mRS 0-1) and early neurological alteration. The safety outcomes were sICH defined according to study criteria and mortality over the study period.

Statistical analysis

Statistical analysis was performed using RevMan5.4 and Stata Software (version 16.0). Absolute counts are provided in addition to effect estimates, which are expressed as risk ratios (RR) with corresponding 95% confidence intervals (CI). The chi-square test was used to analyze

the heterogeneity of the results in each study. All analyses were performed using the random effect model.

Data availability

Data not provided in the article because of space limitations may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

RESULTS

Study characteristics and quality evaluation

A total of 327 articles were obtained through search, and articles that did not meet the inclusion criteria were excluded by reading the titles, abstracts and full texts (Figure 1). Finally, 2 RCTs and 7 cohort studies met the inclusion criteria, and the basic characteristics were shown in Table 1. A total of 4750 patients were included in this analysis. The RCTs included 1032 patients, of whom 506 patients received IVT treatment, 526 patients received MM. The cohort study included 3718 patients, including 1618 patients received IVT treatment, 2100 patients received MM.

Functional outcomes

2 RCTs and 3 cohort studies reported functional independence (mRS 0-2) (Figure 2), the results all showed that there was no significant difference in improving functional independence (mRS 0-2) of patients with minor non-disabling acute ischemic stroke between MM and IVT (Figure 2A, RR: 1.01, 95% CI 0.98 - 1.04, P = 0.47. Figure 2B, RR: 0.97, 95% CI 0.91 - 1.05, P = 0.46). The heterogeneity of analysis results only included RCTs was very low (I2 = 0%), while the heterogeneity of cohort studies was high (I2 = 60%). The GRADE quality of the RCT evidence was high whereas the GRADE quality of the cohort studies was very low (Figure S2).

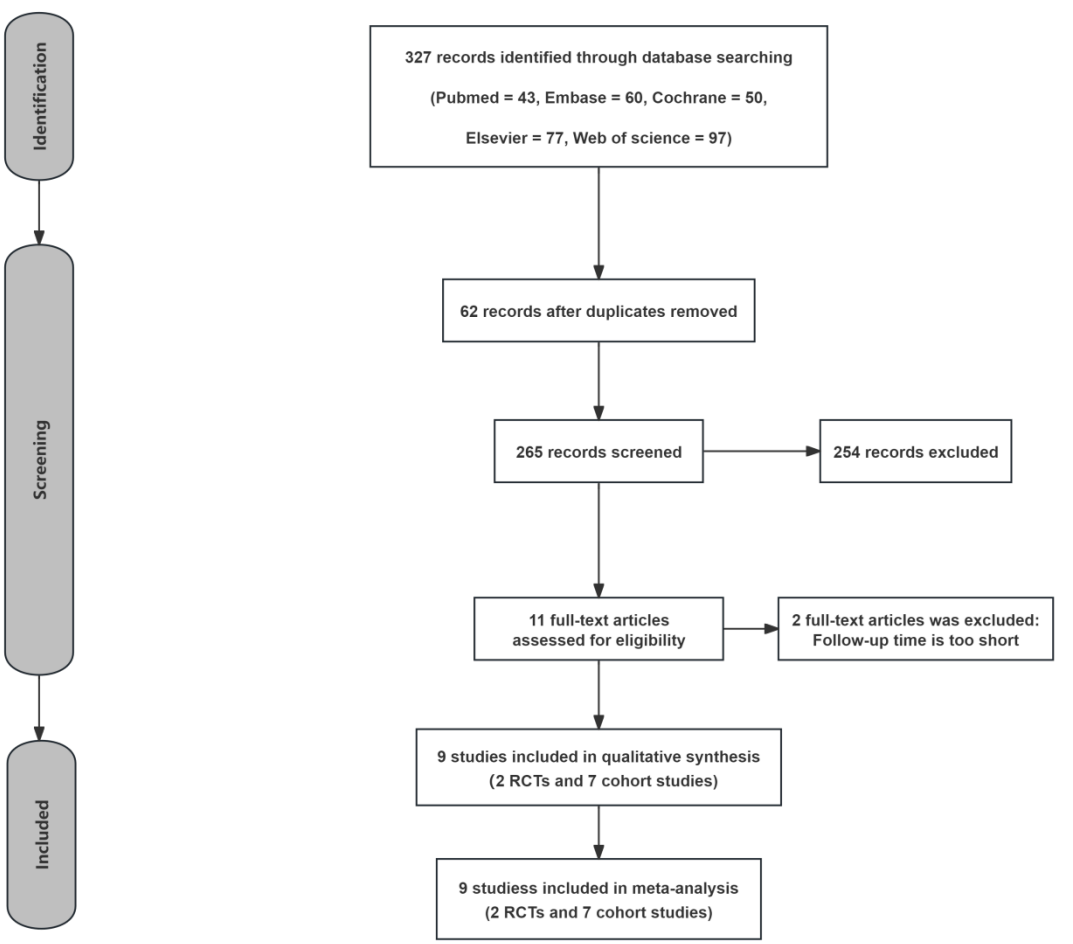


Figure 1. PRISMA flow diagram

Table 1: Characteristics and quality evaluation of included trials

Author and year of publication	Inclusion Criteria	Number of patients	Age	NIHSS score at admission	Stroke to treatment time(min)	Intervention measure	Quality evaluation (Cochrane/NOS)
RCTs							
Hui-Sheng Chen, 2023[19]	NIHSS ≤ 5 and each single item score was ≤ 1	IVT: 350 MM: 369	64 (56-71) 65 (57-71)	2 (1-3) 2 (1-3)	180 (127-225) 182 (134-230)	IVT group: Alteplase 0.9mg/Kg, antiplatelet treatment beginning 24 hours after IVT MM group: 300mg of clopidogrel on the first day, followed by 75 mg per day for 12 ±2 days; 100 mg of aspirin on the first day, followed by 100 mg daily for 12±2 days; and single antiplatelet therapy or DAPT based on guidelines until 90 days	As shown in **Figure e-1**
Pooja Khatri 2018[24]	NIHSS ≤ 5 and deficits judged to not be clearly disabling at presentation	IVT: 156 MM: 157	62 (14) 61 (13)	2.3 (1.2) 2.0 (1.2)	162 (132-174) 168 (144-186)	IVT group: Alteplase 0.9mg/Kg with a placebo oral aspirin MM group: Oral aspirin, 325 mg, with placebo intravenous alteplase	As shown in **Figure e-1**
Cohort studies							
Duan, C, 2023[26]	NIHSS ≤ 5 and each single item score was ≤ 1	IVT: 199 MM: 978	/ / /	/ / /	/ / /	IVT group: Alteplase 0.9mg/Kg MM group: Aspirin at a dose of 100 mg per day, plus clopidogrel at an initial dose of 75 mg or 300 mg, followed by 75 mg per day or Aspirin only (A dose of 100 mg per day	5☆
Guang-hua Li, 2020[32]	Non-disabling stroke and NIHSS ≤ 4	IVT: 43 MM: 47	60.14 (10.01) 60.87 (9.95)	2.81 (1.08) 2.55 (1.12)	/ /	IVT group: Alteplase 0.9mg/Kg, antiplatelet treatment beginning 24 hours after IVT for 10 days MM group: Aspirin at a dose of 100 mg per day, clopidogrel at a dose of 75 mg per day	8☆

Author and year of publication	Inclusion Criteria	Number of patients	Age	NIHSS score at admission	Stroke to treatment time(min)	Intervention measure	Quality evaluation (Cochrane/NOS)
Giovanni Merlino, 2023[33]	NIHSS ≤ 5 and each single item score was ≤ 1	IVT: 175	71 (60-79)	3 (2-4)	/	IVT group: Alteplase 0.9mg/Kg with a maximum dose of 90 mg	8☆
		MM: 144	70 (59-79)	1 (0.25-2)	/	MM group: Aspirin 300 mg or clopidogrel 300 mg within the first 24 h after the onset, followed by a maintenance dose (aspirin 100 mg or clopidogrel 75 mg)	
Wansi Zhong, 2021[34]	NIHSS ≤ 5 and each single item score was ≤ 1	IVT: 241	68 (12)	3 (2-3)	126.5 (76-173)	IVT group: No mentioned.	8☆
		MM: 221	70 (14)	1 (1-2)	120 (83.5-203.5)	MM group: No mentioned.	
Xiaopan Cao, 2023[35]	Non-disabling stroke and NIHSS ≤ 5	IVT: 638	63 (7)	2.3 (1.3)	124.7 (70.9)	IVT group: Alteplase 0.9mg/Kg with a maximum dose of 90 mg or 0.6mg/Kg with a maximum dose of 60 mg.	8☆
		MM: 314	67 (11)	1.5 (1.3)	127.7 (75.1)	MM group: dual antiplatelets, single antiplatelet agent or systemic anticoagulation.	
Huang Hui, 2019[36]	Non-disabling stroke and NIHSS ≤ 5	IVT: 54	/	/	/	IVT group: Alteplase 0.9mg/Kg with a maximum dose of 90 mg	5☆
		MM: 41	/	/	/	MM group: No mentioned.	
Dan Wang, 2024[37]	NIHSS ≤ 5 and isolated symptoms	IVT: 268	64.1 (12.0)	2.2 (0.8)	/	IVT: Alteplase 0.9mg/Kg with a maximum dose of 90 mg.	7☆
		MM: 355	60.3 (12.0)	1.4 (1.1)	/	MM: Aspirin 100 mg and clopidogrel 300 mg within the first 24 h after the onset, followed by a maintenance dose (aspirin 100 mg and clopidogrel 75 mg).	

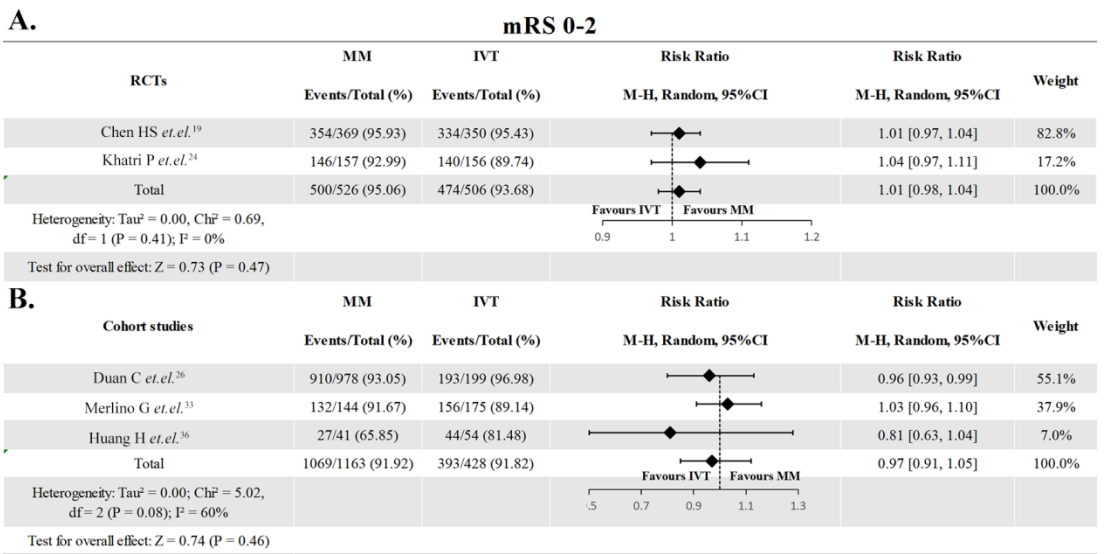


Figure 2. The result of mRS 0-2 for MM vs. IVT.

The results of merging analysis indicated that there was no difference between MM and IVT in achieving excellent outcome (mRS 0-1), regardless of RCTs (Figure S3, RR: 1.03, 95% CI 0.99 - 1.07, P = 0.17) or cohort studies (Figure S3, RR: 0.99, 95% CI 0.95 - 1.03, P = 0.60). The heterogeneity of RCTs was very low (I2 = 0%) with high GRADE quality, while the heterogeneity of cohort studies was significant (I2 = 52%) with very low GRADE quality (Figure S4).

Early neurological deterioration

2 RCTs and 2 cohort studies reported the data of early neurological deterioration. The analysis results of 2 RCTs showed that there was a correlation between IVT and early neurological deterioration, compared to MM (Figure S5, RR: 0.50, 95% CI 0.30 - 0.82, P = 0.007). The GRADE quality of the result was high (Figure S6). The results of cohort studies indicated that there was no significant difference between IVT and MM in terms of early neurological deterioration (Figure S5, RR: 0.93, 95% CI 0.56 - 1.54, P = 0.77). The GRADE quality of the result was very low (Figure S6).

Safety outcomes

In the analysis of RCTs, compared with the MM group, the incidence of sICH in IVT group is higher, but this is not significant (Figure 3A, RR:0.27, 95%CI:0.04-1.64, P=0.15). However, the cohort studies showed that there was a significant correlation between IVT and sICH (Figure 3B, RR:0.20, 95%CI: 0.06-0.68, P=0.01). The GRADE quality of evidence for the 2 RCTs was moderate and the GRADE quality of evidence for the 4 cohort studies was low (Figure S7). There was no significant difference in mortality between the two groups (Figure 4). The GRADE quality of the RCT evidence was moderate and that of the cohort studies was very low (Figure S8).

Risk of Bias

The publication bias of each analysis was tested using Egger methods, and the results indicated that there was no publication bias in the conclusions (Egger's test P > 0.05, Table e-4).

DISCUSSION

This systematic review and meta-analysis included 2 RCTs and 7 cohort studies, with a total of 4750 patients, evaluating the effectiveness and safety of MM and IVT in patients with acute mild non-disabling stroke. In the analysis of functional outcomes, we found that there was no significant difference between IVT and MM in improving patient functional independence (mRS 0-2) and excellent outcome (mRS 0-1). In pooling analysis of RCTs, the results showed that patients receiving IVT were likely to have early neurological deterioration compared to MM. The cohort studies showed that there was a significant correlation between IVT and sICH, but there was no significant difference in mortality between the two groups.

In general, we excluded acute stroke patients

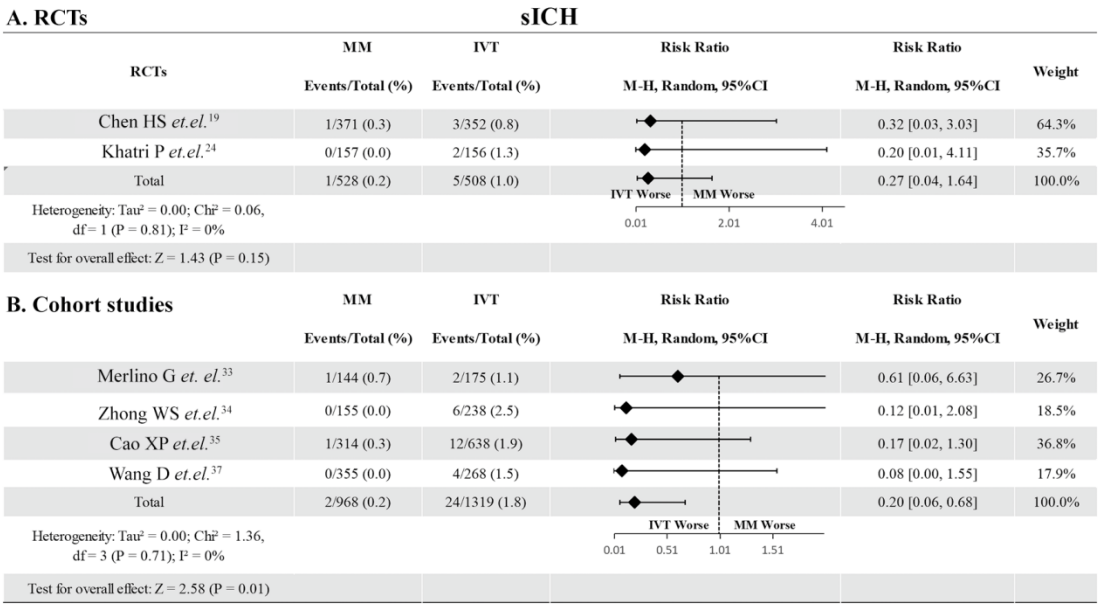


Figure 3. The result of sICH for MM vs. IVT.

with mild symptoms from IVT because their risk of bleeding may outweigh the benefits. However, the patients with low NIHSS scores may still experience long-term disabilities.[23] The PRISMS trail is the first randomized multicenter trial to explore the efficacy and safety of IVT and antiplatelet therapy in patients with acute non-disabling stroke.[24] It was found that compared to aspirin, alteplase therapy did not increase the likelihood of favorable functional outcomes at 90 days, but the very early study termination of the study precluded any definitive conclusions. The recent ARAMIS trial confirms the results of the PRISMS trial, which showed that antiplatelet therapy (dual antiplatelet therapy) was not inferior to alteplase in mild stroke patients without disability, and antiplatelet therapy had a lower risk of sICH.[19]

At present, there is no unified screening criteria for non-disabling stroke. In our study, we found that NIHSS score of ≤ 5, a single score of ≤ 1 and a score of 0 in the consciousness item seem to be a reasonable criterion.[19,25,26] However, the NIHSS score cannot accurately reflect the presence of intracranial artery occlusion, and neurological deterioration usually occurs in patients with

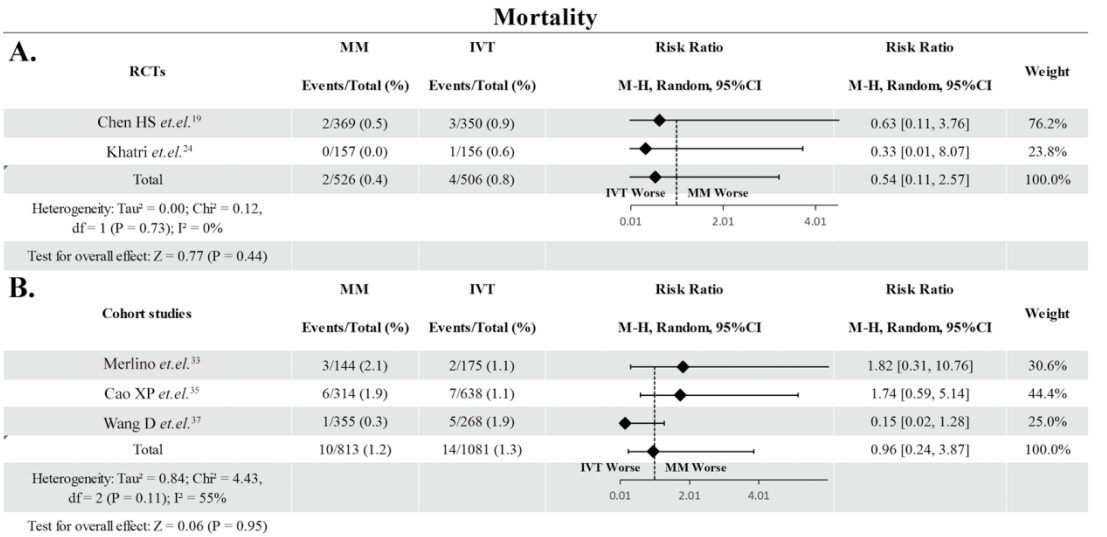


Figure 4. The result of mortality for MM vs. IVT.

severe stenosis of large blood vessels.[27-29] It has been reported that within 3 months after stroke onset, patients with mild neurologic deficit (NIHSS ≤ 5) and large blood vessel occlusion have a higher frequency of deterioration in non-thrombolysis patients than thrombolysis patients.[30] An observational study showed that 24.5% of patients with mild non-disabling stroke have severe stenosis/occlusion, and alteplase therapy can benefit mild non-disabling stroke patients with severe stenosis/occlusion.[30] Thrombolysis caused by alteplase may prevent the initial extension of the thrombus, and even prevent the progression of infarction caused by non-reperfusion. However, the subgroup analysis of ARAMIS showed that the degree of responsible vessel stenosis did not affect the choice of treatment. Compared to IVT, DAPT seemed to be a better choice, although this result was not significant. In addition, the evidence about the necessity of endovascular therapy (EVT) for mild non-disabling AIS patients with large vessel occlusion is lacking and unclear.

Overall, there is no consensus on the treatment of minor stroke, especially minor non-disabling acute ischemic stroke. The American Heart Association/American Stroke Association Guidelines for Early Management of Acute Ischemic Stroke (updated in 2019) and the European Stroke Organization Guidelines for Intravenous Thrombolysis of Acute Ischemic Stroke (updated in 2021) both recommend that patients with acute disabling mild stroke should be treated with intravenous alteplase within the onset time window of 4.5h, but thrombolysis is not recommended for patients with acute non-disabling mild stroke.[20,21] The 2019 edition of the Chinese Clinical Management Guidelines for Ischemic Cerebrovascular Disease recommends intravenous alteplase therapy for acute non disabling mild stroke patients within a 3-hour time window of onset, with evidence level of C.[31] However, our study is more inclined to treat minor non-disabling acute ischemic stroke patients with MM, due to the likelihood of achieving excellent functional outcomes (mRS 0-1) and safety (early neurological deterioration and any bleeding events).

Our systematic review and meta-analysis has limitations. First, the number of RCTs was limited. Second, of the 8 studies included, 6 were conducted in China, which may limit the generalizability of our study results. Third, the treatment methods for the MM group were not uniform, including dual antiplatelet therapy, aspirin alone, and anticoagulant therapy, which may be the major source of heterogeneity in the merge analysis.

In conclusion, for patients with minor non-disabling acute ischemic stroke, MM will not have a negative impact on functional recovery, and may be a safer alternative.

DISCLOSURE

Conflicts of interest: None.

REFERENCES

1. Johnston SC, Amarenco P, Aunes M, *et al*. Ischemic benefit and hemorrhage risk of ticagrelor-aspirin versus aspirin in patients with acute ischemic stroke or transient ischemic attack. *Stroke* 2021;52:3482-9. http://dx.doi.org/10.1161/STROKEAHA.121.035555
2. Johnston SC, Amarenco P, Denison H, *et al*. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Eng J Med* 2020;383:207-17. http://dx.doi.org/10.1056/NEJMoa1916870
3. Johnston SC, Easton JD, Farrant M, *et al*. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Eng J Med* 2018;379:215-25. http://dx.doi.org/10.1056/NEJMoa1800410
4. 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;43:560-2. http://dx.doi.org/10.1161/STROKEAHA.110.593897
5. 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;72:423-31. http://dx.doi.org/10.1001/jamaneurol.2014.4354
6. Wang Y, Meng X, Wang A, *et al*. Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *N Engl J Med* 2021;385:2520-30. http://dx.doi.org/10.1056/NEJMoa2111749
7. Wang Y, Wang Y, Zhao X, *et al*. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Eng J Med* 2013;369:11-19. http://dx.doi.org/10.1056/NEJMoa1215340
8. Dhamoon MS, Moon YP, Paik MC, *et al*. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. *Stroke* 2009;40:2805-11. http://dx.doi.org/10.1161/STROKEAHA.109.549576
9. 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;44:3211-3. http://dx.doi.org/10.1161/strokeaha.113.002881
10. Romano JG, Gardener H, Campo-Bustillo I, *et al*. Predictors of outcomes in patients with mild ischemic stroke symptoms MaRISS. *Stroke* 2021;52:1995-2004. http://dx.doi.org/10.1161/STROKEAHA.120.032809
11. Huisa BN, Raman R, Neil W, Ernstrom K, Hemmen TM. Intravenous tissue plasminogen activator

for patients with minor ischemic stroke. *J Stroke Cerebrovasc Dis* 2012;21:732-6. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2011.03.009
12. Urra X, Ariño H, Llull L, *et al*. The outcome of patients with mild stroke improves after treatment with systemic thrombolysis. *PLoS One* 2013;8. http://dx.doi.org/10.1371/journal.pone.0059420
13. Greisenegger S, Seyfang L, Kiechl S, Lang W, Ferrari J, Austrian Stroke Unit Registry Collaborators. Thrombolysis in patients with mild stroke results from the Austrian Stroke Unit Registry. *Stroke* 2014;45:765-9. http://dx.doi.org/10.1161/STROKEAHA.113.003827
14. Logallo N, Kvistad CE, Naess H, Waje-Andreassen U, Thomassen L. Mild stroke: safety and outcome in patients receiving thrombolysis. *Acta Neurol Scand Suppl* 2014;129:37-40. http://dx.doi.org/10.1111/ane.12235
15. Spokoyny I, Raman R, Ernstrom K, *et al*. Defining mild stroke: Outcomes analysis of treated and untreated mild stroke patients. *J Stroke Cerebrovasc Dis* 2015;24:1276-81. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.01.037
16. Haeberlin MI, Held U, Baumgartner RW, Georgiadis D, Valko PO. Impact of intravenous thrombolysis on functional outcome in patients with mild ischemic stroke without large vessel occlusion or rapidly improving symptoms. *Int J Stroke* 2020;15:429-37. http://dx.doi.org/10.1177/1747493019874719
17. Sykora M, Krebs S, Simader F, *et al*. Intravenous thrombolysis in stroke with admission NIHSS score 0 or 1. *Int J Stroke* 2022;17:109-19. http://dx.doi.org/10.1177/1747493021991969
18. Barber PA Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology* 2001;56:1015-20. http://dx.doi.org/10.1212/wnl.56.8.1015
19. 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;329:2135-44. http://dx.doi.org/10.1001/jama.2023.7827
20. 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:E344-E418. http://dx.doi.org/10.1161/STR.0000000000000211
21. 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:I-LXII. http://dx.doi.org/10.1177/2396987321989865
22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, W264. http://dx.doi.org/10.1136/bmj.b2535
23. 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;42:3110-5. http://dx.doi.org/10.1161/strokeaha.111.613208
24. 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;320:156-66. http://dx.doi.org/10.1001/jama.2018.8496
25. Li ZH, Zhang JG, Xie WZ, et al. Efficacy and safety study of dual antiplatelet versus alteplase in the treatment of acute mild non disabling ischemic stroke. *Chin J Stroke* 2023;18(12):1391-6. http://dx.doi.org/10.3969/j.issn.1673-5765.2023.12.008
26. Duan C, Xiong Y, Gu H, *et al*. Intravenous thrombolysis versus antiplatelet therapy in minor stroke patients with large vessel occlusion. *CNS Neurosci Ther* 2023;29:1615-23. http://dx.doi.org/10.1111/cns.14124
27. Gao Y, Song B, Zhao L, *et al*. Vascular lesion thickness in the lenticulostriate artery region serves as a biomarker for early neurological deterioration. *Curr Neurovasc Res* 2017;14:215-21. http://dx.doi.org/10.2174/1567202614666170621104824
28. Zhou Y, Zhong W, Wang A, *et al*. Hypoperfusion in lenticulostriate arteries territory related to unexplained early neurological deterioration after intravenous thrombolysis. *Int J Stroke* 2019;14:306-9. http://dx.doi.org/10.1177/1747493019830595
29. Coutts SB, O'Reilly C, Hill MD, *et al*. Computed tomography and computed tomography angiography findings predict functional impairment in patients with minor stroke and transient ischaemic attack. *Int J Stroke* 2009;4:448-53. http://dx.doi.org/10.1111/j.1747-4949.2009.00346.x
30. Zhong W, Zhou Y, Zhang K, Yan S, Sun J, Lou M. Minor non-disabling stroke patients with large vessel severe stenosis or occlusion might benefit from thrombolysis. *Brain Sci* 2021;11. http://dx.doi.org/10.3390/brainsci11070945
31. Liu LP, Zhou HZ, Duan WY, *et al*. Chinese Stroke Association guidelines for clinical management of cerebrovascular diseases (2nd Ed) (Excerpt) - Chapter 4 Clinical management of ischaemic cerebrovascular diseases. *Chinese J Stroke* 2023;18(08):910-33. http://dx.doi.org/10.3969/j.issn.1673-5765.2023.08.009
32. Li GH, Zhao Y, Zhao J, Li RX, Wang LH, Dong HB. Efficacy and safety of thrombolysis in treatment of minor stroke. *Chin J Contemp Neurol Neurosurg* 2020;20(10):903-7. http://dx.doi.org/10.3969/j.issn.1672-6731.2020.10.010
33. Merlino G, Nesi L, Vergobbi P, *et al*. The use of alteplase, although safe, does not offer clear clinical advantages when mild stroke is non-disabling. *Front Neurol* 2023;14:1212712. http://dx.doi.org/10.3389/fneur.2023.1212712
34. Zhong W, Zhou Y, Zhang K, Yan S, Sun J, Lou M. Minor non-disabling stroke patients with large vessel severe stenosis or occlusion might benefit from thrombolysis. *Brain Sci* 2021;11:945.
35. Cao XP LJ, Xu B, Xiao Y, Yang T, Sun XH, Sui Y. Best medical management versus intravenous

thrombolysis for mild non-disabling ischemic stroke: a prospective noninferiority registry study. *J Neurol Sci* 2023;451:120706. http://dx.doi.org/10.1016/j.jns.2023.120706

36. Huang H, Chen HY, Yang Y, *et al*. Efficacy analysis of intravenous thrombolysis in patients with mild ischemic stroke. *Chin J Cerebrovasc Dis* 2019;16:231-6. http://dx.doi.org/10.3969/j.issn.1672-5921.2019.05.002
37. Wang D, Wen Q, Liu K, *et al*. Intravenous thrombolysis versus dual antiplatelet therapy in minor ischemic stroke within the thrombolytic window (TAMIS): a multicenter cohort study. *J Thromb Thrombolysis* 2024;57:1172-82. http://dx.doi.org/10.1007/s11239-024-03032-8

Supplementary materials

Supplementary Table 1. Literature search criteria.

(((“Stroke”[Mesh]) OR ((Ischemic Strokes[Title/Abstract]) OR (Stroke, Ischemic[Title/Abstract])) OR (Ischaemic Stroke[Title/Abstract])) OR (Ischaemic Strokes[Title/Abstract])) OR (Stroke, Ischaemic[Title/Abstract])) OR (Cryptogenic Ischemic Stroke[Title/Abstract])) OR (Cryptogenic Ischemic Strokes[Title/Abstract])) OR (Ischemic Stroke, Cryptogenic[Title/Abstract])) OR (Stroke, Cryptogenic Ischemic[Title/Abstract])) OR (Cryptogenic Strokes[Title/Abstract])) OR (Cryptogenic Stroke[Title/Abstract])) OR (Stroke, Cryptogenic[Title/Abstract])) OR (Cryptogenic Embolism Stroke[Title/Abstract])) OR (Cryptogenic Embolism Strokes[Title/Abstract])) OR (Embolism Stroke, Cryptogenic[Title/Abstract])) OR (Stroke, Cryptogenic Embolism[Title/Abstract])) OR (Wake-up Stroke[Title/Abstract])) OR (Stroke, Wake-up[Title/Abstract])) OR (Wake up Stroke[Title/Abstract])) OR (Wake-up Strokes[Title/Abstract])) OR (Acute Ischemic Stroke[Title/Abstract])) OR (Acute Ischemic Strokes[Title/Abstract])) OR (Ischemic Stroke, Acute[Title/Abstract])) OR (Stroke, Acute Ischemic[Title/Abstract])) OR (Strokes[Title/Abstract])) OR (Cerebrovascular Accident[Title/Abstract])) OR (Cerebrovascular Accidents[Title/Abstract])) OR (CVA[Title/Abstract])) OR (Cerebrovascular Accident[Title/Abstract])) OR (CVAs (Cerebrovascular Accident[Title/Abstract]))) OR (Cerebrovascular Apoplexy[Title/Abstract])) OR (Apoplexy, Cerebrovascular[Title/Abstract])) OR (Vascular Accident, Brain[Title/Abstract])) OR (Brain Vascular Accident[Title/Abstract])) OR (Brain Vascular Accidents[Title/Abstract])) OR (Vascular Accidents, Brain[Title/Abstract])) OR (Cerebrovascular Stroke[Title/Abstract])) OR (Cerebrovascular Strokes[Title/Abstract])) OR (Stroke, Cerebrovascular[Title/Abstract])) OR (Strokes, Cerebrovascular[Title/Abstract])) OR (Apoplexy[Title/Abstract])) OR (Cerebral Stroke[Title/Abstract])) OR (Cerebral Strokes[Title/Abstract])) OR (Stroke, Cerebral[Title/Abstract])) OR (Strokes, Cerebral[Title/Abstract])) OR (Stroke, Acute[Title/Abstract])) OR (Acute Stroke[Title/Abstract])) OR (Acute Strokes[Title/Abstract])) OR (Strokes, Acute[Title/Abstract])) OR (Cerebrovascular Accident, Acute[Title/Abstract])) OR (Acute Cerebrovascular Accident[Title/Abstract])) OR (Acute Cerebrovascular Accidents[Title/Abstract])) OR (Cerebrovascular Accidents, Acute[Title/Abstract])) OR (accident, cerebrovascular[Title/Abstract])) OR (acute cerebrovascular lesion[Title/Abstract])) OR (acute focal cerebral vasculopathy[Title/Abstract])) OR (apoplectic stroke[Title/Abstract])) OR (apoplexia[Title/Abstract])) OR (blood flow disturbance, brain[Title/Abstract])) OR (brain attack[Title/Abstract])) OR (brain blood flow disturbance[Title/Abstract])) OR (brain accident[Title/Abstract])) OR (brain insult[Title/Abstract])) OR (brain insultus[Title/Abstract])) OR (cerebral apoplexia[Title/Abstract])) OR (cerebral insult[Title/Abstract])) OR (cerebral vascular accident[Title/Abstract])) OR (cerebral vascular insufficiency[Title/Abstract])) OR (cerebro vascular accident[Title/Abstract])) OR (cerebrovascular arrest[Title/Abstract])) OR (cerebrovascular failure[Title/Abstract])) OR (cerebrovascular injury[Title/Abstract])) OR (cerebrovascular insufficiency[Title/Abstract])) OR (cerebrovascular insult[Title/Abstract])) OR (cryptogenic stroke[Title/Abstract])) OR (cerebrum vascular accident[Title/Abstract])) OR (insultus cerebralis[Title/Abstract])) OR (CVA[Title/Abstract])) OR (ischaemic seizure[Title/Abstract])) OR (ischemic seizure[Title/Abstract])) OR (thrombotic stroke[Title/Abstract]))) AND ((“Thrombolytic Therapy”[Mesh]) OR (((((((((((((((Therapeutic Thrombolysis[Title/Abstract]) OR (Therapeutic Thrombolyses[Title/Abstract])) OR (Thrombolyses, Therapeutic[Title/Abstract])) OR (Thrombolysis, Therapeutic[Title/Abstract])) OR (Therapy, Fibrinolytic[Title/Abstract])) OR (Fibrinolytic Therapies[Title/Abstract])) OR (Therapies, Fibrinolytic[Title/Abstract])) OR (Therapy, Thrombolytic[Title/Abstract])) OR (Therapies, Thrombolytic[Title/Abstract])) OR (Thrombolytic Therapies[Title/Abstract])) OR (Fibrinolytic Therapy[Title/Abstract])) OR (clot lysis[Title/Abstract])) OR (Alteplase[Title/Abstract])) OR (t-PA[Title/Abstract])) OR (Tenecteplase[Title/Abstract])) OR (TNK[Title/Abstract])))) AND (Non disabling*)

CVA = cerebrum vascular accident

Supplementary Table 2. Inclusion and exclusion criteria.

We included published trials that met the following criteria: · Patients clinically diagnosed with acute ischemic stroke and treated within 4.5 hours of stroke symptoms. · Patients with NIHSS score was ≤ 5 and each single item score was ≤ 1. · Patients were divided into thrombolytic therapy group or medical management group. · Study data included patient baseline data (age, occlusion site, NIHSS score, infarct-core volume, interval between time of stroke onset and time of randomization), important efficacy outcomes (90-day mRS, Early neurological improvement, Early neurological deterioration), and safety events (symptomatic intracranial hemorrhage, 90-day mortality). Exclusion criteria: · Articles lacked baseline information or primary study outcomes · There was no control group reported

NIHSS National Institutes of Health Stroke Scale, mRS = modified Rankin scale

Supplementary Table 3. Quality evaluation of the 10 cohort studies.

Author and year of publication	Selection	Comparability	Outcome	Total score
Duan, C, 2023	☆☆☆	Undescribed	☆☆	5☆
Guang-hua Li, 2020	☆☆☆☆	☆☆	☆☆	8☆
Giovanni Merlino, 2023	☆☆☆☆	☆	☆☆☆	8☆
Wansi Zhong, 2021	☆☆☆☆	☆	☆☆☆	8☆
Xiaopan Cao, 2023	☆☆☆☆	☆	☆☆☆	8☆
Huang Hui, 2019	☆☆☆	Undescribed	☆☆	5☆
Dan Wang, 2024	☆☆☆	☆	☆☆☆	7☆

Supplementary Table 4. Publication bias test of each meta analysis.

Meta analysis	Testing methods of publicatoin bias	P
mRS 0-2 (cohort studies)	Egger's Test	0.29
mRS 0-1 (cohort studies)	Egger's Test	0.12
sICH	Egger's Test	0.65
Mortality	Egger's Test	0.27

mRS = modified Rankin scale

Supplementary Figure 1. Quality evaluation of the three randomized trials

Supplementary Figure 2. GRADE summary of mRS 0-2 for MM versus IVT in minor non-disabling acute ischemic stroke

Patient or population: patients with Non-disabling Acute Ischemic Stroke
Settings:
Intervention: MM
Comparison: IVT

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk IVT	Corresponding risk MM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
mRS 0-2 (RCTs)	937 per 1000	946 per 1000 (918 to 974)	RR 1.01 (0.98 to 1.04)	1032 (2 studies)	⊕⊕⊕⊕ high	
mRS 0-2 (Cohort studies)	918 per 1000	891 per 1000 (836 to 964)	RR 0.97 (0.91 to 1.05)	1591 (3 studies)	⊕⊕⊕⊖ very low[1,2]	

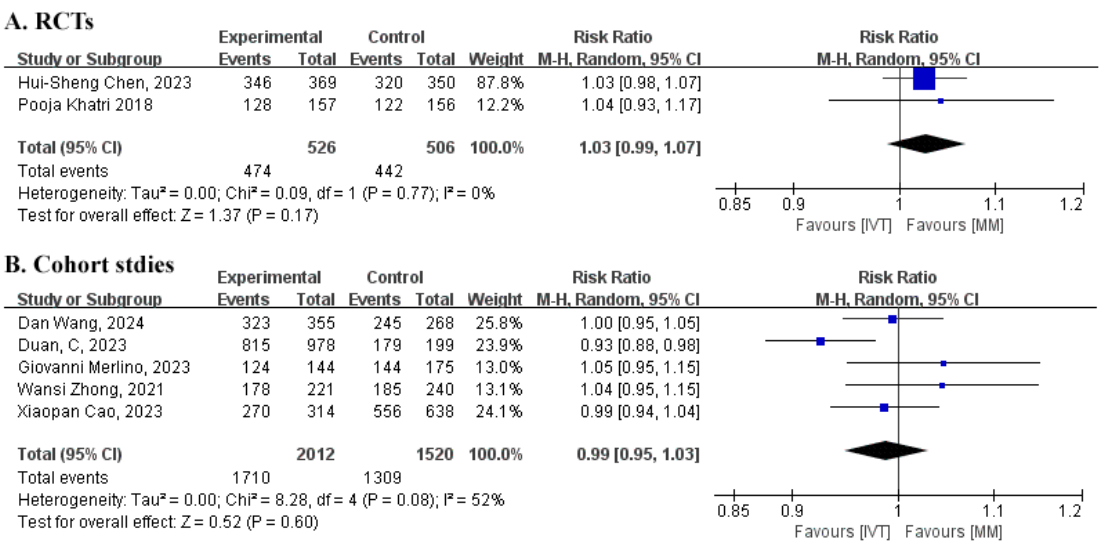
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The heterogeneity of cohort studies was high (I2 = 62%)
[2] The 95%CI range was greater than 0.955-1.045

Supplementary Figure 3. The result of mRS 0-1 for MM vs. IVT.



Supplementary Figure 4. GRADE summary of mRS 0-1 for MM versus IVT in minor non-disabling acute ischemic stroke.

MM compared to IVT for Non-disabling Acute Ischemic Stroke

Patient or population: patients with Non-disabling Acute Ischemic Stroke
Settings:
Intervention: MM
Comparison: IVT

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk IVT	Corresponding risk MM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
mRS 0-1 (RCTs)	874 per 1000	900 per 1000 (865 to 935)	RR 1.03 (0.99 to 1.07)	1032 (2 studies)	⊕⊕⊕⊕ high	
mRS 0-1 (Cohort studies)	861 per 1000	853 per 1000 (818 to 887)	RR 0.99 (0.95 to 1.03)	3532 (5 studies)	⊕⊕⊕⊖ very low[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

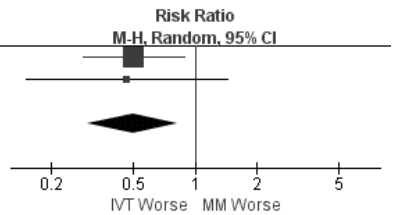
[1] I2 = 63%
[2] The 95%CI range was greater than 0.955-1.045.

Supplementary Figure 5. The result of Early neurological deterioration for MM vs. IVT.

A. RCTs

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hui-Sheng Chen, 2023	17	369	32	350	79.6%	0.50 [0.29, 0.89]
Zhen-hua Li, 2023	4	64	9	67	20.4%	0.47 [0.15, 1.44]
Total (95% CI)		**433**		**417**	**100.0%**	**0.50 [0.30, 0.82]**
Total events	21		41			

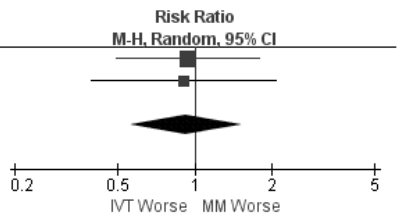
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)



B. Cohort studies

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dan Wang, 2024	20	355	16	268	62.4%	0.94 [0.50, 1.79]
Xiaopan Cao, 2023	8	314	18	638	37.6%	0.90 [0.40, 2.05]
Total (95% CI)		**669**		**906**	**100.0%**	**0.93 [0.56, 1.54]**
Total events	28		34			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)



Supplementary Figure 6. GRADE summary of early neurological deterioration for MM versus IVT in minor non-disabling acute ischemic stroke

MM compared to IVT for Non-disabling Acute Ischemic Stroke

Patient or population: patients with Non-disabling Acute Ischemic Stroke
Settings:
Intervention: MM
Comparison: IVT

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk IVT	Corresponding risk MM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Early neurological deterioration (RCTs)	**98 per 1000**	**49 per 1000** (29 to 81)	**RR 0.50** (0.3 to 0.82)	850 (2 studies)	⊕⊕⊕⊕ **high**	
Early neurological deterioration (Cohort studies)	**38 per 1000**	**35 per 1000** (21 to 58)	**RR 0.93** (0.56 to 1.54)	1575 (2 studies)	⊕⊖⊖⊖ **very low**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The 95%CT range was greater than 0.955-1.045

Supplementary Figure 7. GRADE summary of sICH for MM versus IVT in minor non-disabling acute ischemic stroke.

MM compared to IVT for Non-disabling Acute Ischemic Stroke

Patient or population: patients with Non-disabling Acute Ischemic Stroke
Settings:
Intervention: MM
Comparison: IVT

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk IVT	Corresponding risk MM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
sICH (RCTs)	**10 per 1000**	**3 per 1000** (0 to 16)	**RR 0.27** (0.04 to 1.64)	1036 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
sICH (Cohort studies)	**18 per 1000**	**4 per 1000** (1 to 12)	**RR 0.20** (0.06 to 0.68)	2287 (4 studies)	⊕⊕⊖⊖ **low**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The 95%CI range was greater than 0.955-1.045.

Supplementary Figure 8. GRADE summary of mortality for MM versus IVT in minor non-disabling acute ischemic stroke.

MM compared to IVT for Non-disabling Acute Ischemic Stroke

Patient or population: patients with Non-disabling Acute Ischemic Stroke
Settings:
Intervention: MM
Comparison: IVT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk IVT	Corresponding risk MM				
Mortality (RCTs)	**8 per 1000**	**4 per 1000** (1 to 20)	**RR 0.54** (0.11 to 2.57)	1032 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
Mortality (Cohort studies)	**13 per 1000**	**12 per 1000** (3 to 50)	**RR 0.96** (0.24 to 3.87)	1894 (3 studies)	⊕⊖⊖⊖ **very low**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The 95%CI range was greater than 0.955-1.045.