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Comparing Efficacy and Safety of Dual Antiplatelet Therapy versus Intravenous Thrombolytics in Acute Minor Ischemic Stroke: A Systematic Review and Meta-Analysis

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Abstract

Background: Acute minor ischemic stroke (AMIS) frequently results in significant disability despite current treatment options. This meta-analysis evaluated the effectiveness and safety of dual antiplatelet therapy (DAPT) compared to intravenous thrombolytics (IVT) in treating AMIS. **Methods:** PubMed, Cochrane Central, and ScienceDirect were searched till May 2025. Using a superiority framework, the risk ratios (RRs) along with 95% confidence intervals (CIs) were pooled under a random effects model using the Review Manager version 5.4.1. The quality assessment was done through the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools. The primary and secondary outcomes assessed were functional (excellent and favourable) outcomes, symptomatic intracranial hemorrhage (sICH), recurrent ischemic strokes, all-cause mortality, and early neurological deterioration (END). Publication bias was evaluated via the funnel plots and Egger's regression analysis. **Results:** Six studies pooling 7,366 AMIS patients were included in the meta-analysis. DAPT significantly reduced the END compared to IVT (RR = 0.50; 95%CI:[0.28, 0.89]; p = 0.02). The functional outcomes, including excellent (RR = 0.97; 95%CI: [0.87, 1.07]; p = 0.52) and favourable (RR = 1.00; 95%CI:[0.97, 1.03]; p = 0.97) functional outcomes, were comparable between DAPT and IVT. Likewise, the safety endpoints including sICH (RR = 0.27; 95%CI:[0.05, 1.38]; p = 0.12), recurrent ischemic strokes (RR = 0.89; 95%CI:[0.59, 1.34]; p = 0.59) and all-cause mortality (RR = 0.51; 95%CI:[0.21, 1.23]; p = 0.13) showed no significant difference between the two groups. **Conclusion:** DAPT is associated with lower END rates than IVT in AMIS management. Both groups showed similar efficacy regarding the functional outcomes. Safety outcomes, including sICH, recurrent stroke, and mortality, also showed no significant difference.

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Introduction

Acute minor ischemic stroke (AMIS) comprises up to half of all ischemic strokes. The American Stroke Association (ASA) defines a stroke as 'minor' by a National Institutes of Health Stroke Scale (NIHSS) score of ≤5.[1,2] However, around one-third of patients end up with long-term disability at 90 days due to progression or recurrent strokes.[3] Currently, there are inconclusive guidelines and debate over the preferred therapeutic treatment strategy for patients, particularly those who present within the thrombolytic time window (≤4.5 hours of symptom onset).[4,5]

Intravenous thrombolysis (IVT) is a key acute management technique for acute ischemic stroke (AIS); it produces early arterial recanalization and allows reperfusion to take place, avoiding infarction.[6] According to current guidelines, it is recommended for eligible patients with presenting symptoms within 4.5 hours of onset[7,8] and many meta-analyses have assessed their efficacy and safety.[9,10] However, timely administration is still a challenge clinically due to a lack of recognition of symptoms, leading to the optimal time window being missed, limiting IVT's potential benefits[11,12] although there is ongoing research to assess the IVT beyond the therapeutic window of 4.5 hours.[13-15] Also, many trials exclude low NIHSS score patients, leading to a knowledge gap and poor understanding of the efficacy and safety of IVT in the treatment of mild neurological defects.[16,17] Additionally, variability in trial results regarding IVT efficacy compared to antiplatelet therapy leads to uncertainty in deciding management.[3,5]

Another treatment option that has shown great benefit is dual antiplatelet therapy (DAPT), with aspirin and clopidogrel. Trials such as CHANCE and POINT have demonstrated that it can reduce stroke recurrence in patients with minor stroke or high-risk transient ischemic attack (TIA).[18,19] Guidelines recommend patients starting DAPT within 24 hours of symptom onset, with early therapy shown to prevent further vascular events and superior effects on functional outcomes compared with monotherapy.[7,20,21]

Due to inconsistencies in current evidence and a lack of consensus regarding optimal treatment strategy, a systematic comparison of DAPT and IVT is needed to inform clinical decision-making. This meta-analysis aims to determine whether DAPT offers better efficacy and safety than IVT in treating patients with AMIS. We reviewed current evidence to assess outcomes, including primary efficacy outcomes (excellent and favourable functional outcomes), the primary safety outcome of symptomatic intracranial hemorrhage (sICH), and secondary outcomes such as recurrent ischemic attacks, early neurological deterioration (END), and all-cause mortality.

Methods

Protocol and Reporting Standards

This meta-analysis was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*[22] and adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.[23] The protocol of this review was registered on PROSPERO under the ID: CRD420251116251.

Search Strategy and Data Sources

We conducted a comprehensive electronic search in PubMed, Cochrane Central, and ScienceDirect till May 2025. The search strategy included these terms: "minor stroke," "acute minor ischemic stroke," "mild stroke," "intravenous thrombolysis," "dual antiplatelet therapy," "aspirin," "clopidogrel," and "DAPT." No language restrictions were applied.

Manual screening of references from included studies and prior meta-analyses was also performed to identify additional relevant studies. The complete search strategies used in different electronic databases are provided in Supplemental Table 1.

Eligibility Criteria and Study Selection

Eligible studies included those involving adult patients (≥18 years) with AMIS, defined by an NIHSS score of ≤5. The interventions considered were IVT and early DAPT, typically aspirin plus clopidogrel. "Early DAPT" was defined as DAPT started within 24 hours of symptom onset. Although all studies included in this meta-analysis met this criterion, the onset-to-

treatment (OTT) window varied. Three studies used an OTT window of ≤4.5 hours, while the other three extended the OTT window up to 24 hours. The study types included randomized controlled trials (RCTs), cohort studies, or non-randomized observational studies that directly compared IVT and DAPT. Studies were included if they reported any of the assessed outcomes.

All search results were imported into EndNote software for screening. Two reviewers (F.S. and M.R.S.) independently screened titles and abstracts for relevance. Full texts of potentially eligible studies were reviewed for inclusion. Discrepancies were resolved by a senior author (M.H.W.). The study selection process is detailed in the PRISMA flow diagram (Figure 1).

Data Extraction and Endpoint Definitions

Two reviewers (T.R. and A.A.) independently extracted study data using a pre-designed standardized Excel sheet. The baseline variables extracted were first author name, publication year, study design, location, AMIS definitions, stroke localization, IVT agent, sample size, mean age, sex distribution, baseline NIHSS score, stroke OTT window, and history of previous stroke.

The outcomes extracted were excellent functional outcome at 3 months, sICH, favourable functional outcome at 3 months, recurrent ischemic stroke at 3 months, all-cause mortality at 3 months, and END. The excellent functional outcome is defined as the modified Rankin Scale (mRS) score of 0-1, whereas the good functional outcome is defined as the mRS score of 0-2.

Quality Assessment

This meta-analysis included five non-randomized observational studies and one RCT. The non-randomized observational studies were evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool.[24] The ROBINS-I tool evaluated observational studies for various biases, including confounding bias, classification bias of interventions, bias in participant selection, bias from deviations in the intended intervention, bias due to missing data, bias in outcome measurement, and bias in the selection of reported results. The RCT was assessed with the Cochrane Collaboration's Risk of Bias tool, version 2.0 (RoB 2.0).[25] The RoB 2.0 tool evaluated the RCT across five domains: bias in the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The traffic light plots for both the Cochrane ROBINS-I and RoB 2.0 tools are shown in Figure 2.

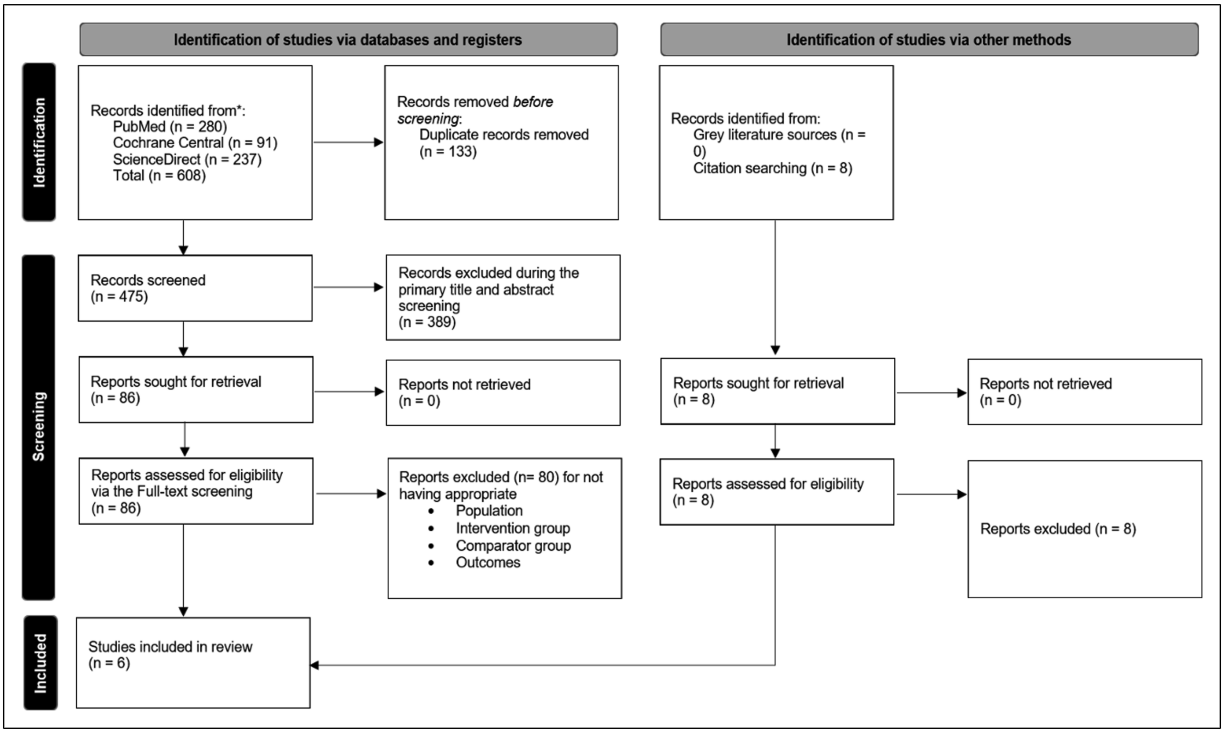

Figure 1. PRISMA flowchart of the study selection process

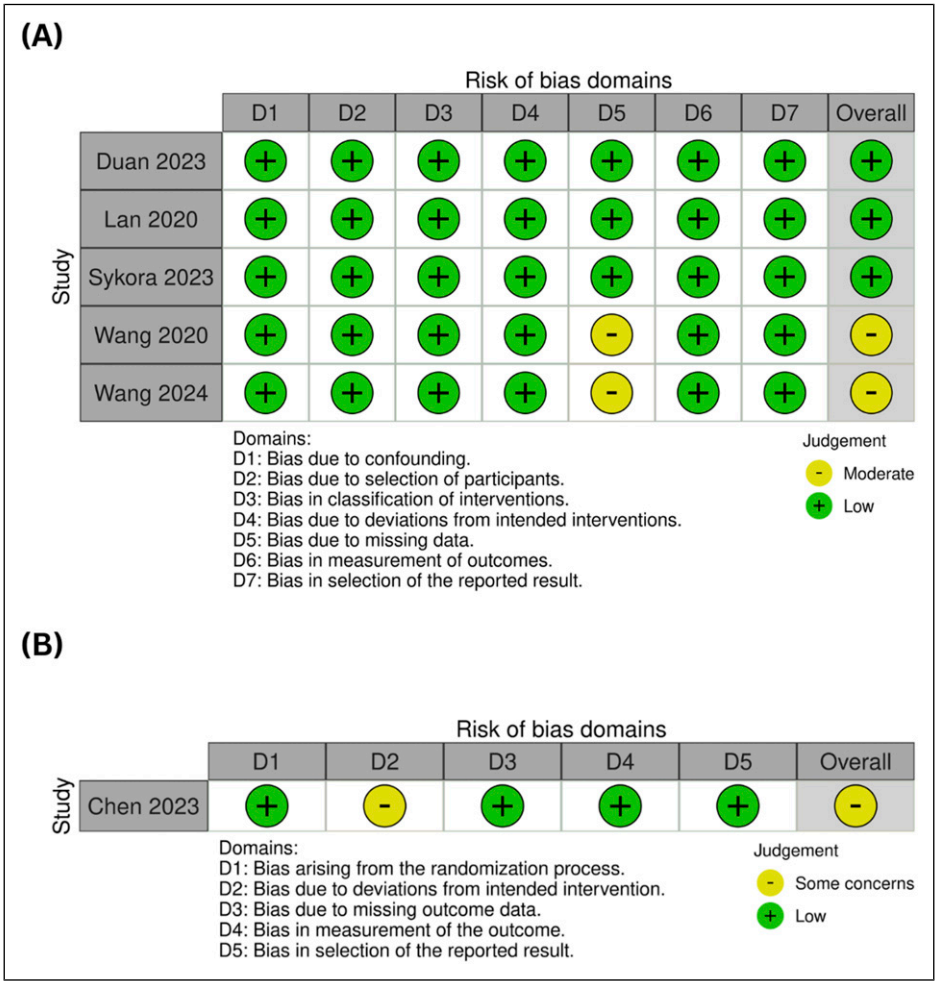

Figure 2. Traffic plots for (A) ROBINS-I tool (B) RoB 2.0 tool

Statistical Analysis

Meta-analysis was conducted using Review Manager (RevMan version 5.4.1). Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed using the Cochrane Q test and Higgins I^2 statistics,[26] with I^2 >50% indicating moderate to high heterogeneity. When heterogeneity was more than 50%, a leave-one-out sensitivity analysis was performed to explore the source of heterogeneity. Subgroup analysis was performed according to the study design (observational studies or RCTs), the NIHSS score cutoff used to define AMIS (≤5 or ≤3), and the time from stroke symptom onset to DAPT treatment window (≤4 hours or ≤24 hours). Publication bias was assessed visually via the funnel plots and confirmed statistically by the Egger's regression test performed using the Comprehensive Meta Analysis software version 3.0.

Results

Initially, the literature search retrieved 608 articles. After removal of duplicates (n=133), 475 unique articles remained. After screening the titles and abstracts, 389 articles were excluded, leaving 86 studies for full-text screening against the eligibility criteria. Ultimately, six studies[12,27-31] were included in this meta-analysis. The study selection process is detailed in Figure 1.

Study Characteristics

This meta-analysis included six studies[12,27-31] (one RCT and five cohort studies), thus most of the evidence compiled is derived from the observational cohort studies. Across six studies, five[12,27-29,31] from China and one[30] from Austria, published

between 2020 and 2024, 7,366 patients with AMIS were analyzed. All the studies used a cutoff of NIHSS ≤5 to define the AMIS, except two,[12,30] which used NIHSS ≤3. The mean age ranged from 61 to 71 years. Median baseline NIHSS clustered at 2–3, and almost all patients were treated within 4.5 h of onset, except for the three studies which extended the DAPT window to 24.[12,29,30] Alteplase at 0.9 mg/kg was administered as the IVT agent in all included studies, while the aspirin and clopidogrel combination was used as DAPT. Only two of the included studies involved patients with large vessel occlusion[28,31] and reported data on both disabling and non-disabling strokes, while Chen et al[27] only provided data on non-disabling strokes; other studies did not report this parameter. The patients with prestroke mRS 0-1 score ranged from 10.5% to 100%. The incidence of the previous stroke ranged from 14.4% to 23.4%. The DAPT group exhibited a higher prevalence of previous strokes (Duan 2023: 23.4% compared to 17.5%; Sykora 2023: 22.4% versus 16.1%) and consisted of slightly older patients in the largest cohort (Sykora 2023: 71 versus 68 years). This may introduce bias, favoring the IVT group. Additionally, most included studies show that the IVT group has a greater proportion of patients with prestroke mRS scores of 0-1, which could further bias the results in favor of IVT. The baseline characteristics for the included studies are summarized in Table 1.

Bias Assessment

Among the six included studies, five were non-randomized and assessed using the ROBINS-I tool, while one RCT was evaluated using the Cochrane RoB 2.0 tool. Duan et al. 2023, Lan et al. 2020, and Sykora et al. 2023 were judged to have low risk of bias across all domains.[28-30] Wang 2020 and Wang 2024 exhibited a moderate risk of bias,[12,31] mainly in the domain of "bias due to missing data" (D5). The only randomized trial, Chen 2023,[27] generally had a low risk of bias across most domains, but there were some concerns overall, particularly regarding "bias due to deviations from the intended intervention" (D2). While the overall methodological quality is acceptable, the moderate risk of bias from missing data and deviations from the intended intervention may contribute to the heterogeneity seen in the pooled estimates.

Outcomes

A detailed summary of the meta-analysis is provided in Table 2.

Excellent Functional Outcome

The outcome was reported by six studies with a total of 5,147 patients (DAPT 3,103 vs IVT 2,044). The DAPT and IVT groups did not show any significant difference regarding excellent functional outcome (RR 0.97; 95%CI: 0.87, 1.07; p = 0.52). The heterogeneity was found to be high (I^2 = 94%) (Figure 3).

Symptomatic Intracranial Hemorrhage

The outcome of sICH was reported by 5 studies with 6,390 patients (3,854 DAPT vs 2,536 IVT). The analysis showed that the two groups were comparable regarding sICH (RR 0.27; 95%CI: 0.05-1.38; p= 0.12). A high heterogeneity was detected (I^2 = 72%) (Figure 4).

Favourable Functional Outcome

Four studies reported this outcome with 2,505 patients in these studies (1,418 DAPT vs 1,087 IVT). The analysis showed no significant difference between the two groups regarding favourable functional outcome (RR 1.00; 95%CI: 0.97-1.03; p = 0.97; I^2 = 49%) (Figure 5).

Recurrent Ischemic Stroke

This outcome was reported by three studies with 2,227 patients (1,375 DAPT vs 852 IVT). The two groups were comparable with a pooled effect of (RR 0.89; 95%CI: 0.59-1.34; p= 0.59, I^2= 0%) (Figure 6).

Table 1. Baseline Characteristics of the Included Studies

Studies	Countries	Study design	AMIS definition	Localization	IVT agent	No. of patients	Age in years	Female n (%)	Admission NIHSS	OTT (hours)	Prestroke mRS 0-1 n (%)	Previous stroke n (%)
							Mean (SD)					
Chen 2023	China	RCT	NIHSS ≤ 5	AC + PC	Alteplase 0.9 mg/kg	IVT n=350 DAPT n=369	IVT= 64.3 ± 10.4 DAPT=63.7 ± 11.1	IVT n=110 (31.4) DAPT n=113(30.6)	IVT= 2 (1-3) DAPT= 2 (1-3)	IVT= ≤4.5 DAPT= ≤4.5	IVT n= 350 (100) DAPT n= 369 (100)	IVT n=77 (22.0) DAPT n= 82 (22.2)
Duan 2023	China	PO-NR	NIHSS ≤ 5	AC + PC	Alteplase 0.9 mg/kg	IVT n=251 DAPT n=722	IVT= 61.7 ± 9.6 DAPT= 63.0 ± 10.4	IVT n=73 (29.1) DAPT n=212 (29.4)	IVT= 3 (2-4) DAPT= 2 (1–4)	IVT= ≤4.5 DAPT= ≤4.5	IVT n= 237 (94.4) DAPT n=653 (90.4)	IVT n=44 (17.5) DAPT n=169 (23.4)
Lan 2020	China	RO-NR	NIHSS ≤ 5	N/A	Alteplase 0.9 mg/kg	IVT n=109 DAPT n=119	IVT= 63.0 ± 41.5 DAPT= 60.7 ± 40.0	IVT n=35 (32.1) DAPT n=33 (27.7)	IVT= 4 (1-5) DAPT= 2.5 (0-5)	IVT= ≤4.5 DAPT= ≤4.5 or ≤24	-	IVT n=18 (16.5) DAPT n=22 (18.5)
Sykora 2023	Austria	PO-NR	NIHSS ≤ 3	AC + PC	Alteplase 0.9 mg/kg	IVT n=1,195 DAPT n=2,625	IVT= 68.1 ± 14.0 DAPT= 70.8 ± 12.0	IVT n=444 (37.2) DAPT n=1,016 (38.7)	IVT= 2 (0-3) DAPT= 1 (0-3)	IVT= ≤4.5 DAPT= ≤24	IVT n=1,099 (92) DAPT n=2,351(89.7)	IVT n= 192 (16.1) DAPT n=588 (22.4)
Wang 2020	China	RO-NR	NIHSS ≤ 3	-	Alteplase 0.9 mg/kg	IVT n=385 DAPT n=215	IVT= 61.3 ± 11.1 DAPT= 63.4 ± 11.9	IVT n=128 (33.2) DAPT n=66 (30.7)	IVT= 2 (1-3) DAPT= 2 (1-3)	IVT= ≤4.5 DAPT= ≤4.5 or ≤24	IVT n=334 (86.8) DAPT n=175 (81.4)	IVT n=65 (16.9) DAPT n= 42 (19.5)
Wang 2024	China	AO-NR	NIHSS ≤ 5	AC + PC	Alteplase 0.9 mg/kg	IVT n=492 DAPT n=534	IVT= 64.7 ± 12.0 DAPT= 60.5 ± 12.2	IVT n=349 (70.9) DAPT n=393 (73.6)	IVT= 2.9 ± 1.2 DAPT= 2.1 ± 1.5	IVT= ≤4.5 DAPT= ≤4.5	IVT n=52 (10.5) DAPT n= 244 (45.7)	IVT n=75 (15.2) DAPT n=77 (14.4)

AC, anterior circulation; PC, posterior circulation; IVT, intravenous thrombolysis; DAPT, dual antiplatelet therapy; AMIS, acute minor ischemic stroke; SD, standard deviation; NIHSS, national institutes of health stroke scale; OTT, onset to treatment; mRS, modified Rankin scale; RCT, randomized controlled trial; PO-NR, prospective non-randomized; RO-NR, retrospective non-randomized; AO-NR, ambispective non-randomized; Note that most of the evidence compiled is derived from the observational cohort studies.

Table 2. Summary of Meta-Analysis

Endpoint	Studies	Sample size			Effect size (RR)	95% CI		P Value	Heterogeneity			
		Overall	DAPT	IVT		Lower limit	Upper limit		Tau^2	Chi^2	*df*	I^2 (%)
Excellent Functional Outcome												
Core Analysis												
	6	5,147	3,103	2,044	0.97	0.87	1.07	0.52	0.02	80.24	5	94
Subgroup Analysis												
Observational Studies	5	4,428	2,734	1,694	0.95	0.83	1.09	0.49	0.02	77.38	4	95
RCTs	1	719	369	350	1.03	0.98	1.07	0.23	-	-	-	-
NIHSS ≤ 5	4	2,938	1,737	1,201	1.02	0.97	1.08	0.42	0	10.67	3	72
NIHSS ≤ 3	2	2,209	1,366	843	0.82	0.46	1.45	0.49	0.17	66.34	1	98
OTT ≤4.5 hr	3	2,710	1,618	1,092	1.00	0.96	1.04	0.93	0	4.02	2	50
OTT ≤24 hr	3	2,437	1,485	952	0.92	0.65	1.31	0.65	0.09	76.76	2	97
Symptomatic Intracranial Hemorrhage												
Core Analysis												
	5	6,390	3,854	2,536	0.27	0.05	1.38	0.12	1.91	10.78	3	72
Subgroup Analysis												
Observational Studies	4	5,667	3483	2184	0.25	0.03	2.14	0.21	2.80	10.78	2	81
RCTs	1	723	371	352	0.32	0.03	3.03	0.32	-	-	-	-
NIHSS ≤ 5	3	1,977	1,014	963	0.90	0.24	3.36	0.88	0.22	1.26	1	20
NIHSS ≤ 3	2	4,413	2,840	1,573	0.08	0.03	0.26	<0.0001	0	0.03	1	0
OTT ≤4.5 hr	2	1,749	905	844	0.90	0.24	3.36	0.88	0.22	1.26	1	20
OTT ≤24 hr	3	4,641	2,949	1,692	0.08	0.03	0.26	<0.0001	0	0.03	1	0
Favourable Functional Outcome												
Core Analysis												
	4	2,505	1,418	1,087	1.00	0.97	1.03	0.97	0	5.85	3	49
Subgroup Analysis												
Observational Studies	3	1,786	1,049	737	1.00	0.96	1.04	0.98	0	5.42	2	63
RCTs	1	719	369	350	1.01	0.97	1.04	0.74	-	-	-	-
NIHSS ≤ 5	3	1,912	1203	709	1.01	0.97	1.04	0.66	0	4.52	2	56
NIHSS ≤ 3	1	593	215	378	0.97	0.93	1.02	0.26	-	-	-	-
OTT ≤4.5 hr	2	1,684	1084	600	1.00	0.97	1.02	0.69	0	0.93	1	0
OTT ≤24 hr	2	821	334	487	1.01	0.93	1.10	0.74	0	4.82	1	79
Recurrent Ischemic Stroke												
Core Analysis												
	3	2,227	1,375	852	0.89	0.59	1.34	0.59	0	1.66	2	0
Subgroup Analysis												
Observational Studies	3	2,227	1,375	852	0.89	0.59	1.34	0.59	0	1.66	2	0
RCTs	-	-	-	-	-	-	-	-	-	-	-	-
NIHSS ≤ 5	-	-	-	-	-	-	-	-	-	-	-	-
NIHSS ≤ 3	-	-	-	-	-	-	-	-	-	-	-	-
OTT ≤4.5 hr	2	1,999	1,256	743	0.94	0.62	1.42	0.77	0	0.09	1	0
OTT ≤24 hr	1	228	119	109	0.23	0.03	2.02	0.18	-	-	-	-
All-cause Mortality												
Core Analysis												
	4	3,313	1,840	1,473	0.51	0.21	1.23	0.13	0	1.93	3	0
Subgroup Analysis												
Observational Studies	3	2,592	1,471	1,121	0.47	0.17	1.30	0.15	0	1.874	2	0
RCTs	1	721	369	352	0.64	0.11	3.78	0.62	-	-	-	-
NIHSS ≤ 5	3	2,720	1,625	1,095	0.53	0.21	1.32	0.17	0	1.88	2	0
NIHSS ≤ 3	1	593	215	378	0.35	0.02	7.28	0.50	-	-	-	-
OTT ≤4.5 hr	3	2,720	1,625	1,095	0.53	0.21	1.32	0.17	0	1.88	2	0

(continued)

Table 2. (continued)

Endpoint	Studies	Sample size			Effect size (RR)	95% CI		P Value	Heterogeneity			
		Overall	DAPT	IVT		Lower limit	Upper limit		Tau^2	Chi^2	*df*	I^2 (%)
OTT ≤24 hr	1	593	215	378	0.35	0.02	7.28	0.50	-	-	-	-
Early Neurological Deterioration												
Core Analysis												
	3	5,565	3,528	2,037	0.50	0.28	0.89	0.02	0.20	8.84	2	77
Subgroup Analysis												
Observational Studies	2	4,846	3,159	1,687	0.50	0.20	1.24	0.13	0.39	8.84	1	89
RCTs	1	719	369	350	0.50	0.29	0.89	0.02	-	-	-	-
NIHSS ≤ 5	2	1,745	903	842	0.66	0.43	1.01	0.06	0.03	1.53	1	35
NIHSS ≤ 3	1	3,820	2,625	1,195	0.31	0.20	0.48	<0.00001	-	-	-	-
OTT ≤4.5 hr	2	1,745	903	842	0.66	0.43	1.01	0.06	0.03	1.53	1	35
OTT ≤24 hr	1	3,820	2,625	1,195	0.31	0.20	0.48	<0.00001	-	-	-	-

Note. RCT: Randomized controlled trial; NIHSS: National Institute of Health Stroke Scale; OTT: Onset to treatment time; DAPT: Dual antiplatelet therapy; IVT: Intravenous thrombolysis; RR: Risk ratio; CI: Confidence interval; *df*: Degree of freedom

All-Cause Mortality

This outcome was reported by four studies, with 3,313 patients in these studies (1,840 DAPT vs 1,473 IVT). The analysis showed no significant differences among the two groups with a pooled effect size of (RR: 0.51; 95%CI: 0.21-1.23; p = 0.13; I^2 = 0%) (Figure 7).

Early Neurologic Deterioration

This endpoint was reported by three studies with 5,565 patients (3,528 DAPT vs 2,037 IVT). The analysis showed a statistically significant decrease in END in the DAPT group with a pooled effect size of (RR 0.50; 95%CI: 0.28-0.89; p = 0.02). The heterogeneity observed was high (I^2 = 77%) (Figure 8).

Subgroup Analysis

Subgroup analysis was conducted based on the study design (observational studies or RCTs), the cutoff of NIHSS score used to define the AMIS (≤5 or ≤3), and the OTT window for DAPT (≤4.5 hours or ≤24 hours).

On subgrouping according to study design, the results of the individual subgroups remained consistent with overall pooled results (Figures 3-5A and 7A), except the results of END became insignificant (p = 0.13) in the observational studies subgroup (Figure 8A).

In subgroup analysis based on the NIHSS score cutoff used to define the AMIS, the results for individual subgroups generally remained consistent with the overall pooled results (Figures 3B,5B, and 7B), except that the sICH became significantly decreased in the DAPT arm when the NIHSS score of ≤ 3 was taken to define AMIS (Figure 4B). Similarly, the decrease in the END in the DAPT arm remained significant only when the NIHSS benchmark to define AMIS was taken ≤ 3, whereas it became insignificant for the benchmark of ≤5 (Figure 8B).

On subgrouping according to the time window of initiating DAPT from the onset of stroke symptoms, the results remained consistent with the overall results across all endpoints (Figures 3C and 5-7C), except that the sICH became significantly decreased in the DAPT arm when the OTT was ≤24 hours (Figure 4C). Similarly, the decrease in the END in the DAPT arm remained significant only when the OTT was ≤24 hours, whereas it became insignificant when the OTT was ≤4.5 hours (Figure 8C).

However, it is important to note that the results of most subgroup analyses are based on small numbers of studies, so they should be interpreted with caution rather than considered conclusive.

Sensitivity Analysis

A leave-one-out sensitivity analysis was conducted to explore sources of heterogeneity in outcomes with substantial inconsistency. For excellent functional outcome, the heterogeneity significantly decreased from 94% to 73% upon exclusion

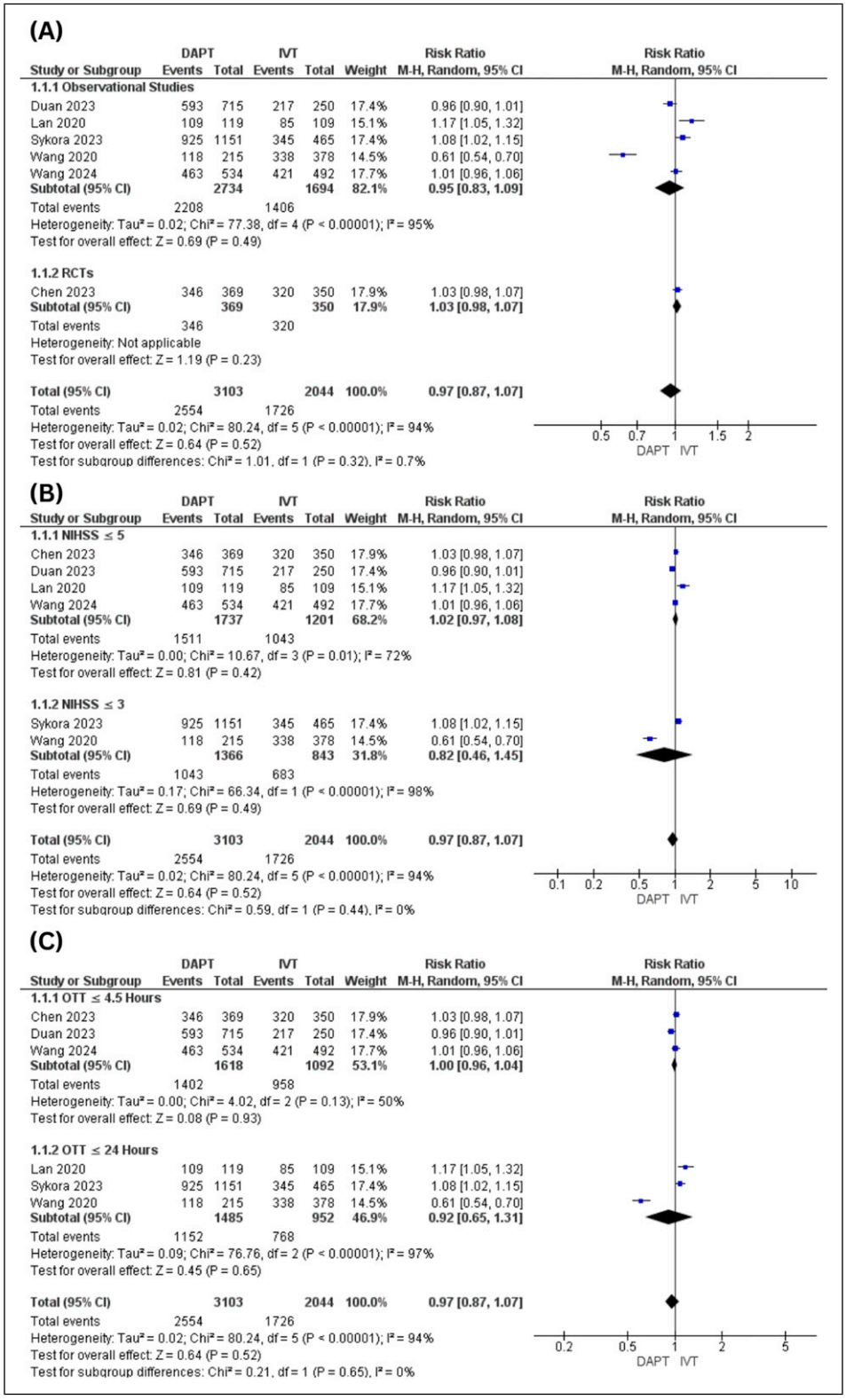

Figure 3. Excellent functional outcome (A) subgroup analysis based on the study design (B) subgroup analysis based on the National Institute of Health Stroke Scale (NIHSS) cutoff defining the AMIS (C) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

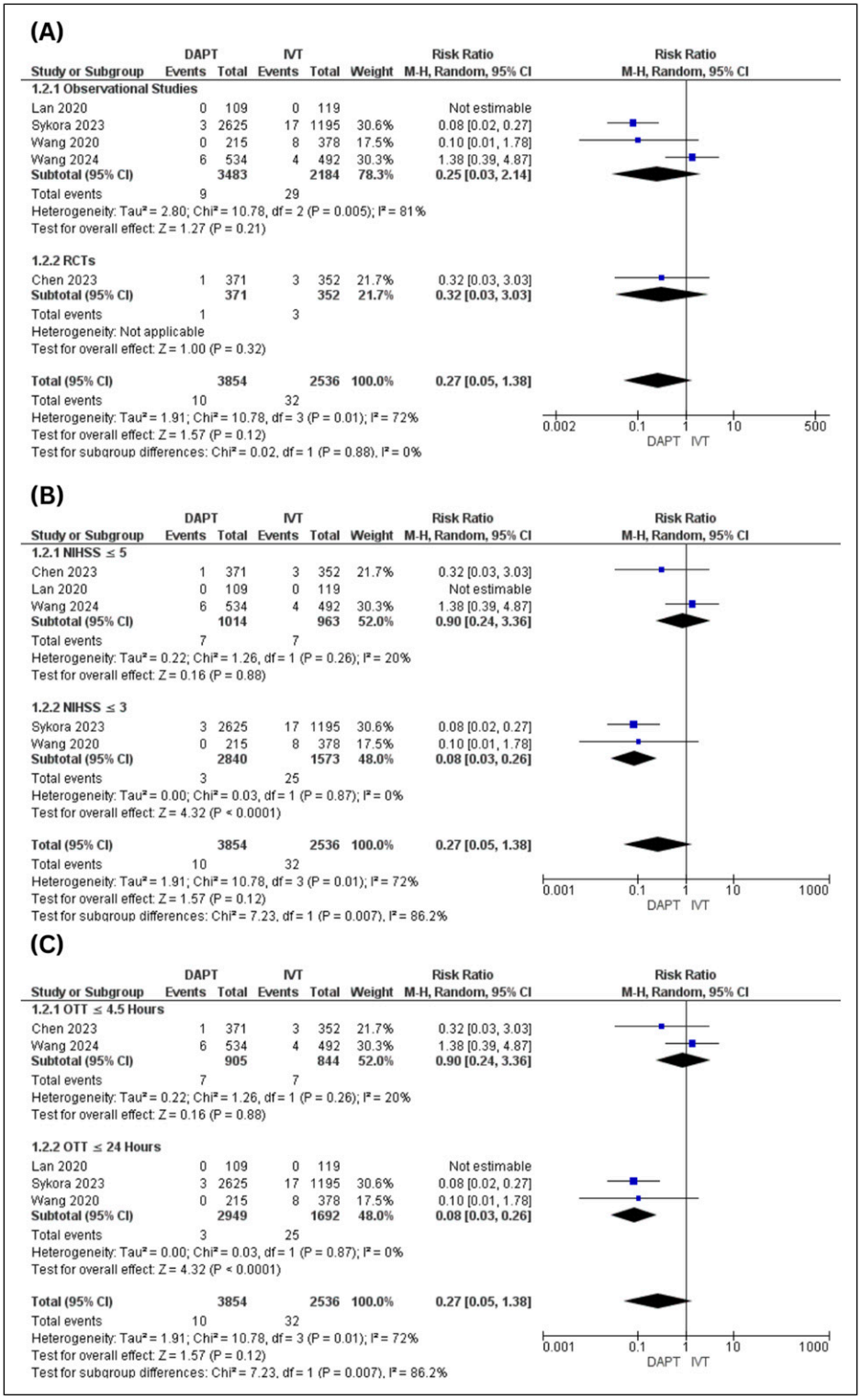

Figure 4. Symptomatic intracranial hemorrhage (A) subgroup analysis based on the study design (B) subgroup analysis based on the National Institute of Health Stroke Scale (NIHSS) cutoff defining the AMIS (C) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

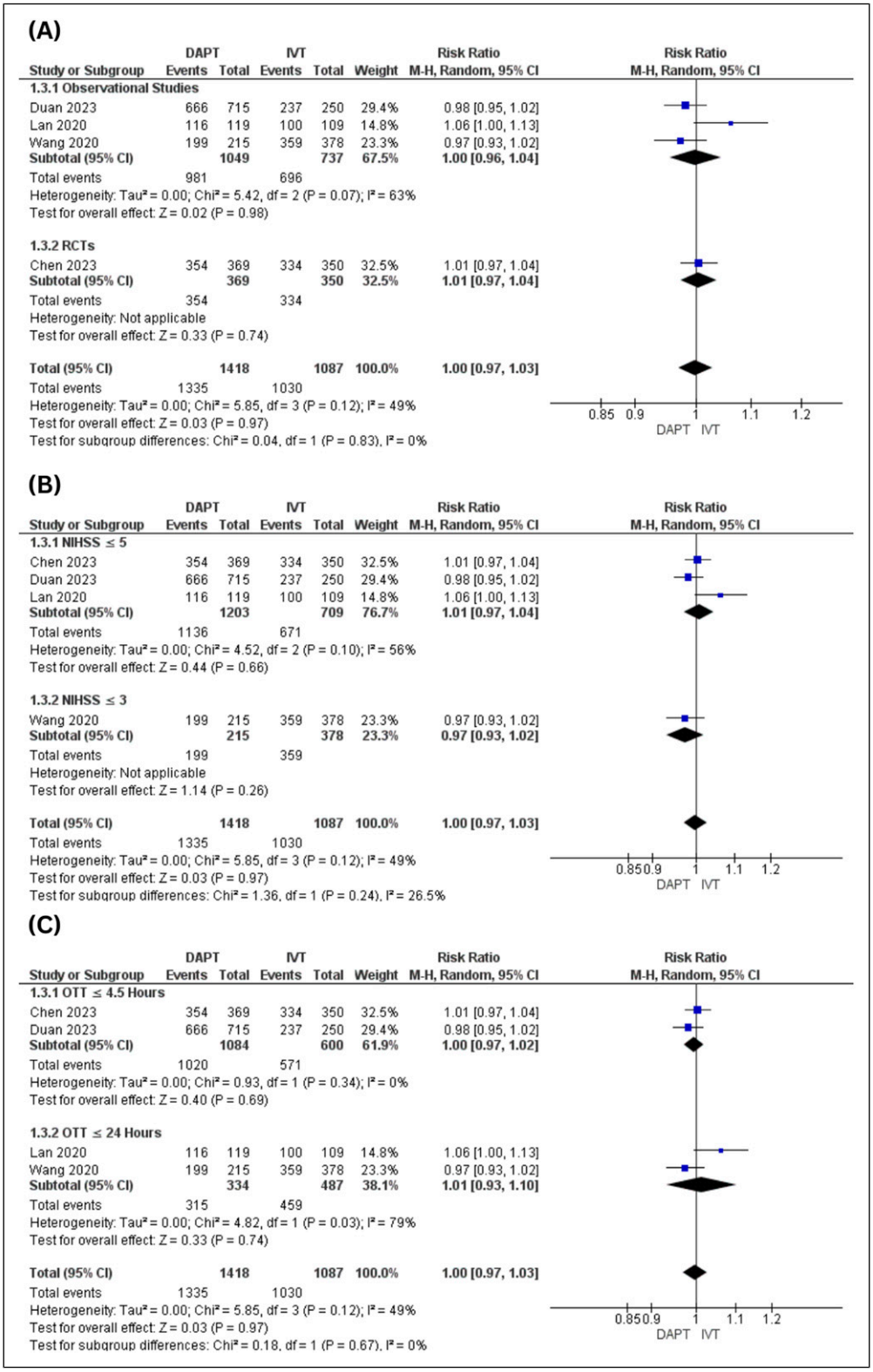

Figure 5. Favourable functional outcome (A) subgroup analysis based on the study design (B) subgroup analysis based on the National Institute of Health Stroke Scale (NIHSS) cutoff defining the AMIS (C) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

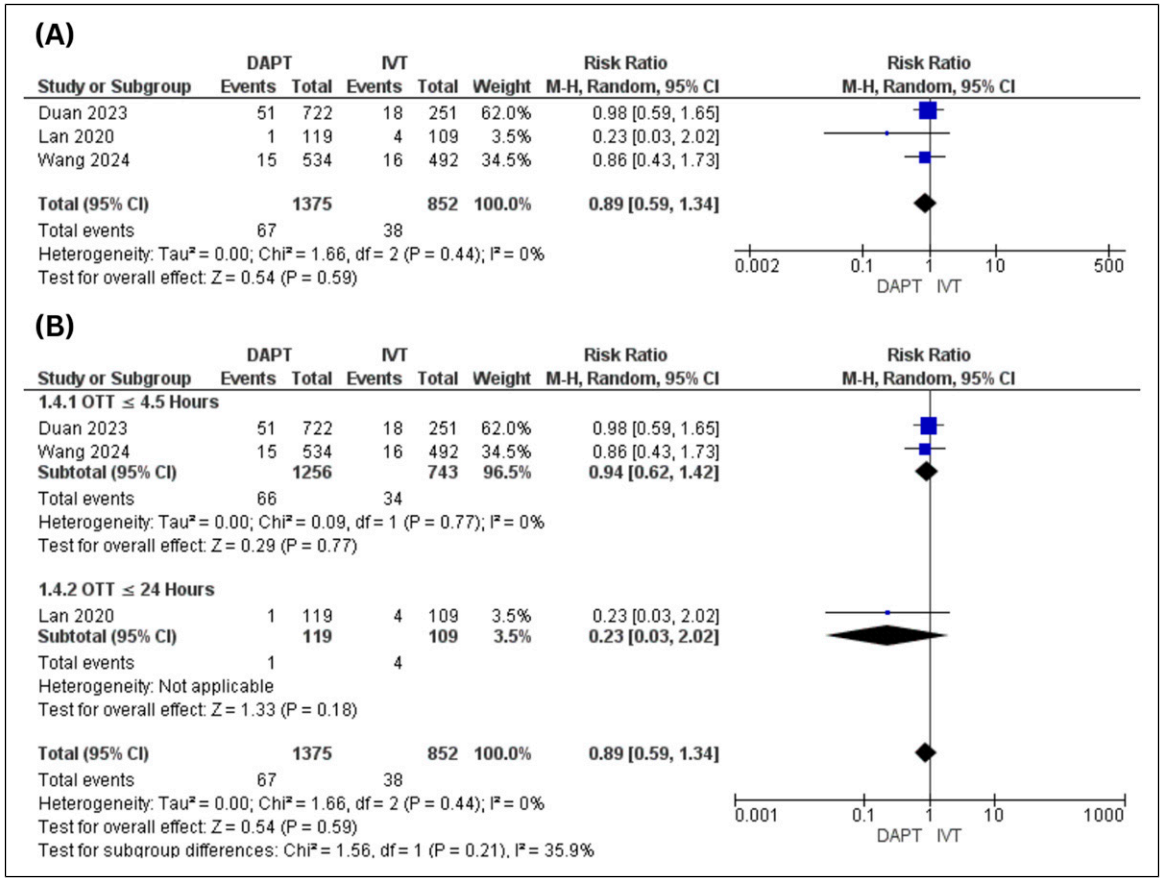

Figure 6. Recurrent ischemic stroke (A) core analysis forest plot (B) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

of Wang et al. (2020)[12] (Supplemental Figure 1). In the case of sICH, heterogeneity dropped from 72% to 0% after the removal of Wang et al. (2024)[31] (Supplemental Figure 2). Similarly, for END, heterogeneity was reduced from 77% to 35% after omitting Sykora et al. (2023)[30] (Supplemental Figure 3).

Publication Bias

Publication bias was assessed through visual inspection of funnel plots for each outcome. The distribution of studies appeared symmetrical around the pooled effect estimates, with no substantial asymmetry observed. This suggests a low likelihood of publication bias influencing the results. While funnel plots are a qualitative method, the consistent symmetry across all analyzed outcomes reinforces the robustness of the findings. This was further confirmed by performing Egger's regression test (Supplemental Figures 4–14) except for the recurrent ischemic stroke endpoint, for which the Egger's regression test showed significant (Intercept = -1.71; p = 0.03) publication bias (Supplemental Figure 15). However, it must be noted that these publication bias assessment tests are inherently underpowered due to the small number of studies (n = 6) included in this meta-analysis. Therefore, the results of these tests should be interpreted cautiously, especially regarding the recurrent ischemic stroke endpoint.

Discussion

This meta-analysis examined the clinical outcomes of AMIS treated with IVT or DAPT. Mainly based on observational data, our results suggest that DAPT is comparable to IVT in achieving functional outcomes (both excellent and favorable) at 3 months, as well as regarding the rates of sICH, all-cause mortality, and recurrent ischemic stroke. Although DAPT was linked to a lower incidence of END, these findings are primarily from observational studies and are subject to potential confounding. Consequently, these results should be viewed as hypothesis-generating rather than conclusive.

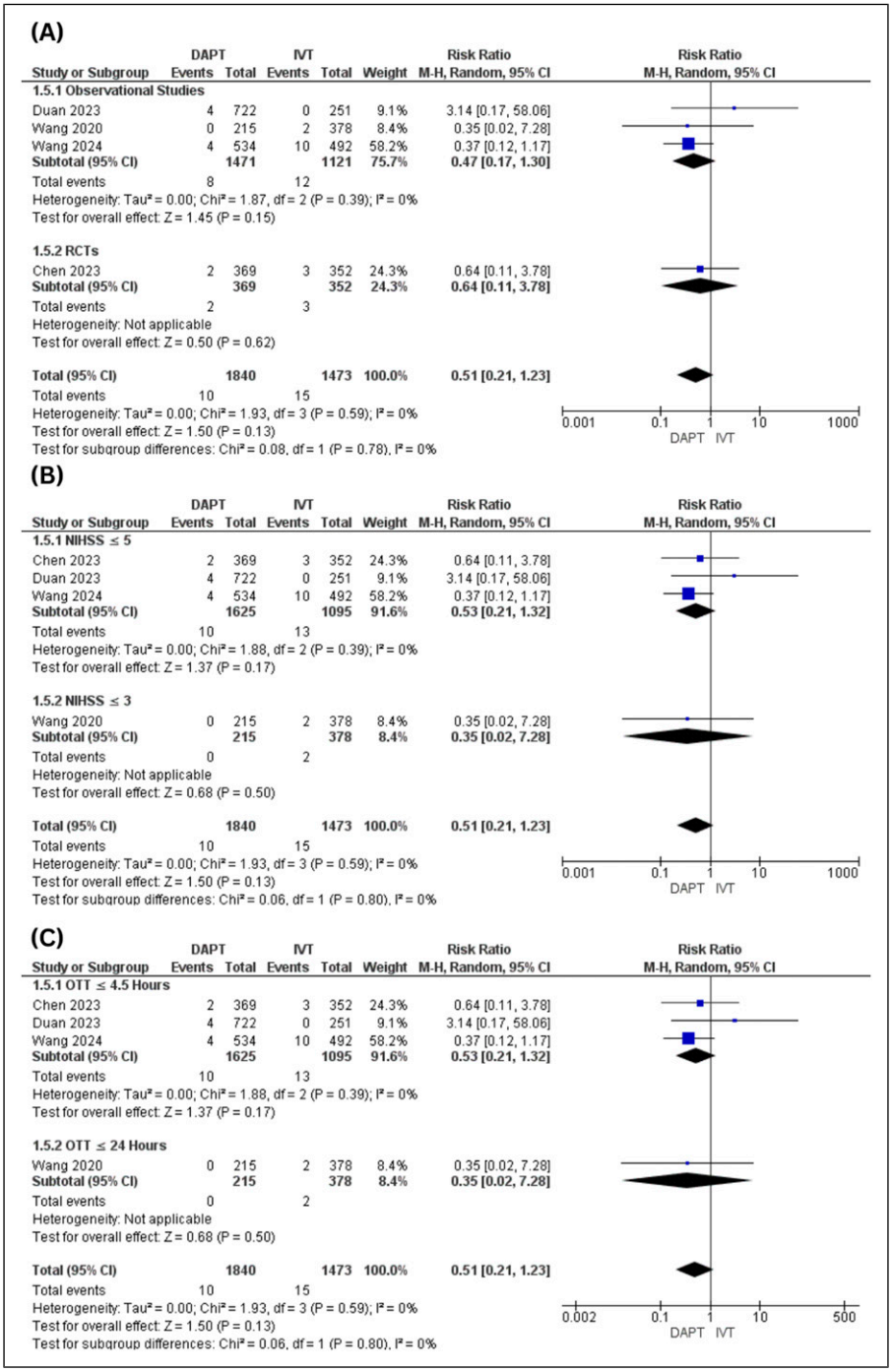

Figure 7. All-cause mortality (A) subgroup analysis based on the study design (B) subgroup analysis based on the National Institute of Health Stroke Scale (NIHSS) cutoff defining the AMIS (C) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

While Abbas et al. (2024)[32] reported a significant reduction in sICH with DAPT, our analysis did not find a significant difference. This is likely due to our larger and more recent dataset, offering a more statistically robust and cautious estimate of bleeding risk. Furthermore, our study builds on Abbas et al.'s[32] work by showing DAPT's benefits against END and examining additional outcomes, such as recurrent ischemic stroke risk, offering a more comprehensive safety profile. We also performed detailed subgroup analyses based on the NIHSS score cutoff for defining the AMIS (≤5 or ≤3) and the OTT window for DAPT (≤4.5 hours or ≤24 hours), which Abbas et al[32] did not include.

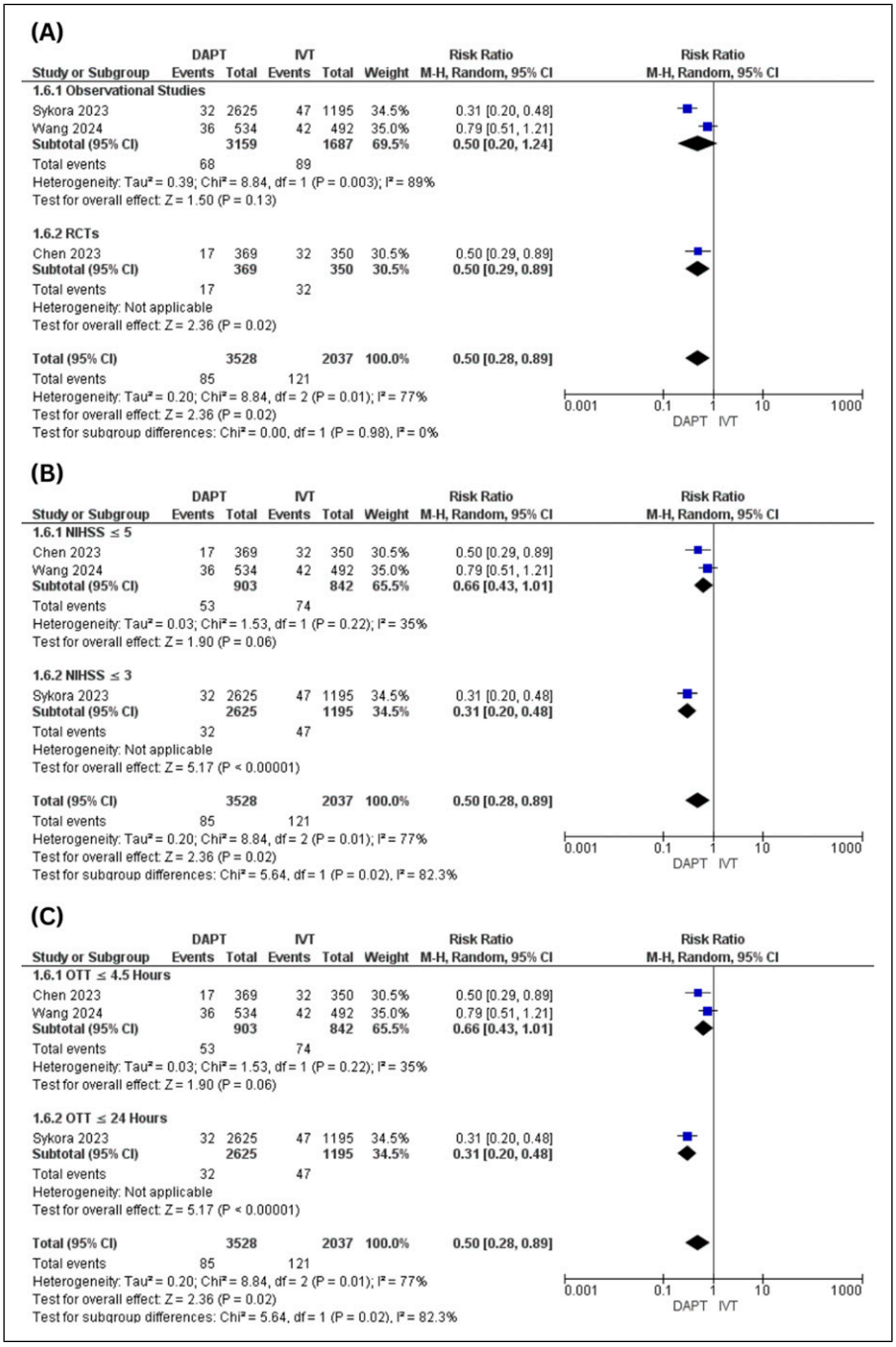

Figure 8. Early neurological deterioration (A) subgroup analysis based on the study design (B) subgroup analysis based on the National Institute of Health Stroke Scale (NIHSS) cutoff defining the AMIS (C) subgroup analysis based on the onset to treatment time (OTT) window for delivering Dual antiplatelet therapy (DAPT)

The PRISMS trial was the first study to compare IVT with a single antiplatelet therapy (SAPT); however, its results were not conclusive (5). The efficacy of IVT has been shown in multiple non-randomized studies, such as Sykora et al (2023) and You et al (2018).[30,33] But there is limited data regarding its efficacy as compared to DAPT. In contrast to this, DAPT has shown promising results for treating AMIS, especially concerning the prevention of further ischemic events.[21] The POINT trial reported that DAPT has also shown superiority to SAPT in this regard. However, it has a higher risk of hemorrhage as compared to SAPT.[19] Therefore, there is a comprehensive need to compare IVT versus DAPT in terms of efficacy in treating AMIS.

Our study showed that IVT was not superior to DAPT in patients with AMIS, especially in terms of excellent and favourable functional outcomes at 3 months. Moreover, our results also showed that the incidence of recurrent ischemic stroke was similar across both groups in 3 months. These findings are consistent with a meta-analysis by Qin et al., which reported similar results, stating the non-superiority of IVT to DAPT.[17] These results could be attributed to the fact that IVT has a relatively short half-life with rapid clearance from circulation. This limits its ability for sustained antithrombotic effect and allows possible thrombus progression/reoccurrence.[27]

DAPT was associated with a lower incidence of END as compared to IVT. Similar results have been reported in other studies as well.[12,17] This occurs because IVT offers only a short-term benefit secondary to its half-life of only a couple of minutes. This leaves the thrombus vulnerable to progression or recurrence.[34]

In terms of safety profile, although the results were insignificant, the risk of a sICH was far lower in DAPT than in IVT. This is because sICH is a known side effect of IVT due to its fibrinolytic mechanism.[35] These results are in coherence with the literature published online as well.[12,30] However, our pooled results on sICH conflict with Qin et al.'s findings,[17] which indicated a significant reduction in sICH incidence in the DAPT group. The DAPT group had almost half the mortality as compared to the IVT group; however, it was non-significant. Similar results were also reported by Wang et al[31] and Qin et al.[17]

Our study has some limitations as well. Our meta-analysis has a fair share of observational studies, contributing to selection bias. The etiology of strokes was not reported in some studies. Although we defined "early DAPT" as starting DAPT within 24 hours of symptom onset, variations in the OTT window across included studies (≤4.5 hours and ≤24 hours) may contribute to heterogeneity. Similarly, there was heterogeneity in the NIHSS score cutoff defining the AMIS. Additionally, five of the six included studies were conducted in China, which could limit the generalizability and applicability of our findings to other regions. Since most included studies are observational, treatment allocation in these studies was likely influenced by the physician's preferences and baseline stroke severity rather than random assignment, which may introduce residual confounding. We assessed only the use of alteplase as IVT; the efficacy of tenecteplase, reteplase, and other thrombolytic agents remained to be explored.

Conclusion

DAPT is linked to lower END rates compared to IVT in managing AMIS. The efficacy outcomes, such as excellent and favourable functional outcomes at 3 months, were similar across both groups. Likewise, safety outcomes, including sICH, recurrent ischemic stroke, and all-cause mortality at 3 months, showed no significant differences between the DAPT and IVT groups. These findings should be viewed with caution, and there is a need for large sample size RCTs to confirm them.

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Declaration of Conflicting Interests

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Data Availability Statement

Data can be obtained by reasonable request directed to the authors.

Supplemental Material

Supplemental material for this article is available online.

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