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REVIEW ARTICLE

Intravenous thrombolysis before mechanical thrombectomy for acute ischemic stroke due to large vessel occlusion; should we cross that bridge? A systematic review and meta-analysis of 36,123 patients

Hazem S. Ghaith[1,2] · Mohamed Elfil[2,3] · Mohamed Diaa Gabra[2,4] · Asmaa Ahmed Nawar[2,5] · Mohamed Sameh Abd-Alkhaleq[2,6] · Khaled M. Hamam[2,6] · Lara Ebrahim Aboelnasr[2,7] · Esraa Ayman Elgezery[2,8] · Mohamed Hosny Osman[2,5] · Hanaa Elsayed[2,5] · Sarya Swed[2,9] · Ulrick Sidney Kanmounye[2,10] · Ahmed Negida[2,5,11,12]

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Abstract

Background The use of intravenous thrombolysis (IVT) before mechanical thrombectomy (MT) for acute ischemic stroke due to large vessel occlusion (AIS-LVO) is a debatable subject in the field of neuro-interventional surgery. We conducted this systematic review and meta-analysis to synthesize evidence from published studies on the outcomes of IVT + MT compared with MT alone in AIS-LVO patients.

Methods We searched PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials from inception to January 2022 for relevant clinical trials and observational studies. Eligible studies were identified, and all relevant outcomes were pooled in the meta-analysis DerSimonian-Liard random-effects model.

Results Forty-nine studies, with a total of 36,123 patients, were included in this meta-analysis. IVT + MT was significantly superior to MT alone in terms of successful recanalization (RR 1.06, 95% CI 1.03 to 1.09), mortality (RR 0.75, 95% CI 0.68–0.82), favorable functional outcome (RR 1.21, 95% CI 1.13 to 1.29), and complete recanalization (RR 1.06, 95% CI 1.00 to 1.11). There were no significant differences between the two groups in terms of improvement of the National Institute of Health Stroke Scale (NIHSS) score at 24 h or at discharge ($p > 0.05$). Complications including symptomatic intracranial hemorrhage, symptomatic intracerebral hemorrhage (sICH), procedure-related complications, and parenchymal hematoma were comparable between the two groups ($p > 0.05$).

Conclusion For AIS-LVO, IVT + MT is associated with slightly better rates of survival, successful and complete recanalization, and favorable functional outcome as compared with MT alone. Further clinical trials are needed to corroborate such benefits of bridging IVT.

Keywords Mechanical thrombectomy · Endovascular thrombectomy · Intravenous thrombolysis · Meta-analysis · Systematic review · Acute ischemic stroke

Abbreviations

AIS	Acute ischemic stroke
AIS-LVO	Acute ischemic stroke due to large vessel occlusion
CI	Confidence interval
EVT	Endovascular therapy
IVT	Intravenous thrombolysis
LVO	Large vessel occlusion
MD	Mean difference
MT	Mechanical thrombectomy
mTICI	Modified Thrombolysis in Cerebral Infarction grade
NIHSS	National Institute of Health Stroke Score
RCT	Randomized-controlled trials
RR	Risk Ratio
IV	Inverse variance (meta-analysis method)
M-H	Mantel-Haenszel (meta-analysis method)

Hazem S. Ghaith and Mohamed Elfil have equal contributions as first authors.

✉ Ahmed Negida
ahmed_negida@hms.harvard.edu;
ahmed.said.negida@gmail.com

Extended author information available on the last page of the article

Introduction

The efficacy of intravenous thrombolysis (IVT) has been previously studied in acute ischemic stroke (AIS) patients when given in the strict time window and in the absence of contraindications [1]. However, the efficacy of IVT is limited in AIS patients with large vessel occlusion (AIS-LVO), with only 6–30% of patients achieving successful recanalization [2]. Moreover, IVT might increase the risk of secondary hemorrhage, which limits its applicability in this patient population [3, 4]. On the other hand, mechanical thrombectomy (MT) has provided higher successful recanalization rates and has, therefore, become the standard of care for patients with AIS-LVO who meet the eligibility criteria for endovascular treatment (EVT) [5, 6].

Given the differences between IVT and MT in procedures, time window, and canalization mechanism, investigators sought to investigate whether the use of IVT prior to MT (known as the bridging therapy) provides greater benefit than MT alone. It has been advocated that IVT prior to MT might shorten the time of successful MT by changing the nature of the blood clot, making it more amenable to mechanical intervention, and dissolving the residual thrombotic material [7, 8]. On the other hand, the administration of IVT in combination with MT might increase the risk of intracranial hemorrhage.

According to the American Stroke Association [6], eligible AIS-LVO patients can still receive IVT and undergo MT. Several studies, both randomized clinical trials (RCTs) and observational studies, have compared MT alone with MT + IVT in patients with AIS-LVO, meeting the criteria for both treatment modalities. However, the results of published studies are inconsistent and inconclusive in terms of functional outcome, secondary intracranial hemorrhage, and mortality [8–13].

To date, experts and clinical practice guidelines agree that IVT + MT is statistically superior to MT alone; however, there are some doubts about whether this superiority is significantly sufficient to advocate the use of IVT + MT over MT alone for AIS-LVO. There is a lack of class I evidence on the associated benefits and risks of combining IVT and MT in AIS-LVO compared with MT alone. Therefore, we conducted this systematic review and meta-analysis to synthesize evidence from all published studies on the outcomes of combined bridging therapy and MT compared with MT alone in terms of successful recanalization, complete recanalization, mortality, functional independence, NIH stroke score (NIHSS), and complications.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines during this systematic review and meta-analysis [14]. The methods were done in strict accordance with the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions (version 5.1.0).

Eligibility criteria

We included all studies satisfying the following criteria:

1. *Population:* studies on patients with AIS-LVO
2. *Intervention:* studies where the experimental or exposed group received IVT + MT
3. *Comparator:* studies where the control group received MT alone
4. *Outcome:* we included studies reporting at least one of the following outcomes: mortality rates, successful recanalization, complete recanalization, favorable mRS at 90 days, NIHSS score at baseline, 24 h after the stroke event and/or at discharge from the hospital, onset-to-groin time, procedural time, and complications.
5. *Study design:* studies with comparative designs, whether RCTs or observational studies comparing the outcomes of MT alone with IVT + MT.

We excluded studies that were not in English and studies on either MT alone or MT combined with IVT without direct comparison between both arms.

Literature search

We performed a comprehensive literature search of four electronic databases (PubMed, Scopus, Web of Science, Cochrane CENTRAL) from inception until 1 January 2022 using this search query ("*Mechanical thrombectomy*" OR "*Endovascular thrombectomy*") AND (*Intravenous thrombolysis*" OR *Alteplase*) AND ("*Acute Ischemic Stroke*" OR *AIS*). All duplicates were removed, and all references of the included studies were screened manually for any eligible studies.

Screening of the literature search results

Retrieved results from the literature search were screened in two steps. In the first step, the title and abstracts of all articles were screened for eligibility. Then, the full-text articles of eligible abstracts were retrieved and screened for eligibility.

Data extraction

Data were extracted to a uniform data extraction sheet. The extracted data included (1) characteristics of the included studies, (2) characteristics of the population of included studies, (3) risk of bias domains, and (4) outcome measures.

Outcome measures

In the present meta-analysis, we considered the following outcome measures:

Mortality

Defined as the proportion of patients who died; it is represented as the risk ratio (RR) between the two groups.

Successful recanalization

Defined as the proportion of patients with Thrombolysis in Cerebral Infarction (mTICI) grades 2b-3; it is represented as the RR between the two groups.

Complete recanalization

Defined as the proportion of patients with modified Thrombolysis in Cerebral Infarction (mTICI) grade 3; it is represented as the RR between the two groups.

Functional independence or favorable functional outcome

It is defined as achieving modified Rankin Scale (mRS) score of 0–2; it is represented as the RR between the two groups.

NIHSS (change from baseline)

The NIH stroke score will be presented as the mean difference between the two study groups from baseline to endpoint.

Symptomatic intracerebral hemorrhage

The incidence of symptomatic intracerebral hemorrhage (sICH) will be expressed as the RR between the two groups.

Symptomatic intracranial hemorrhage

The incidence of symptomatic intracranial hemorrhage will be expressed as the RR between the two groups.

Parenchymal hematoma

The incidence of parenchymal hematoma will be expressed as the RR between the two groups.

Procedure-related complications

The incidence of procedure-related complications will be expressed as the RR between the two groups.

Onset-to-groin time (in minutes)

It is defined as the time from onset of stroke to groin puncture; it will be represented as the mean difference between the two study groups.

Procedural time (in minutes)

It is defined as the time from groin puncture to recanalization; it will be represented as the mean difference between the two study groups.

Synthesis of results

For outcomes that constitute continuous data, the mean difference (MD) between the two groups from the baseline to the endpoint, with its standard deviation (SD), were pooled in the DerSimonian-Laird random-effect model. In the case of studies reporting data in multiple time points, we considered the last endpoint for the primary analysis. For outcomes that constitute dichotomous data, the frequency of events and the total number of patients in each group were pooled as relative risk between the two groups in the DerSimonian-Laird random-effect model. All statistical analyses were done by Review Manager software (RevMan, version 5.4) for macOS, StataMP version 17 for macOS, and Open Meta[analyst] for Microsoft Windows.

Heterogeneity assessment

Statistical heterogeneity among studies was evaluated by the Chi-square test (Cochrane Q test). Then, the chi-square statistic, Cochrane Q, was used to calculate the I-squared according to the equation: $I^2 = \left(\frac{Q-df}{Q}\right) \times 100\%$. A Chi-square P value less than 0.1 was considered as significant heterogeneity. I-square values $\geq 50\%$ were indicative of high heterogeneity.

Risk of bias across studies

Two authors independently assessed the quality of included clinical trials in strict accordance with the Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011). We used the quality assessment table provided in (part 2, Chapter 8.5) the same book. For the observational studies, we used New Castle Ottawa Scale (NOS). Any discrepancies between the two assessors were resolved through discussion and including a third assessor. To explore the publication bias across studies, we constructed funnel plots to present the relationship between effect size and standard error. Two methods assessed evidence of publication bias; (1) Egger's regression test and (2) the Begg and Mazumdar rank correlation test (Kendall's tau).

Certainty assessment

We conducted a certainty assessment through sensitivity analysis (also called leave-one-out meta-analysis) to test the evidence's robustness. For every outcome in the meta-analysis, we ran sensitivity analysis in multiple scenarios, excluding one study in each scenario to make sure the overall effect size was not dependent on any single study.

Meta-regression analysis

To test whether the study outcomes were dependent on the onset-to-groin time, we conducted meta-regression analysis models where the effect estimates and the corresponding (standard errors) were plotted against the onset-to-groin time (on the X-axis). The regression coefficient was calculated an omnibus P value of <0.05 was considered for statistical significance. The meta-regression analysis was done by the Open Meta[Analyst] software of Oxford University's Center of Evidence-based Medicine.

Results

Literature search results and study selection

Our literature search process retrieved 2752 records. Following titles and abstract screening, 213 articles were eligible for full-text screening. From these 213 studies, 49 studies were included in the meta-analysis. Also, the references of the included studies were manually searched, and no further articles were included. The flow chart of the study selection process is shown in the PRISMA flow diagram in (Fig. 1).

Study characteristics

The population of the studies was homogenous; all studies enrolled 36,123 patients with AIS-LVO undergoing MT. Four studies were RCTs, while forty-five studies were observational studies. The characteristics of the included studies are summarized in Table 1, while summary and baseline characteristics of populations of these studies are shown in Table 2.

Risk of bias within studies

The quality of included studies ranged from moderate to high quality according to the Cochrane Risk of Bias Assessment tool for the RCTs and the Newcastle Ottawa Scale for the observational studies. The risk of bias summary is shown in Fig. 2 A and B, while the detailed risk of bias in every study is available in Figs. 1S and 2S in the supplementary file.

Mortality

The pooled RR of mortality favoured the IVT + MT group who had significantly fewer mortality events compared with the MT alone group (16.5% vs. 19.7%; RR 0.75, 95% CI [0.68 to 0.82], $p<0.0001$, Fig. 3). The pooled studies were not homogenous ($p=0.02$; $I^2=36\%$). Subgroup analysis of mortality according to the study design showed that the observational studies (0.72, 95% CI [0.65 to 0.80]) but not the RCTs (0.94, 95% CI [0.75 to 1.17]) had statistically significant pooled RR in favor of the IVT + MT group.

Complete and successful recanalization

The pooled RR of successful recanalization favoured the IVT + MT group over MT alone (77.7% vs. 75.9%; RR 1.06, 95% CI [1.03 to 1.09], $p=0.0007$, Fig. 3). The pooled RR of complete recanalization favoured the IVT + MT group over MT alone (RR 1.06, 95% CI [1.01 to 1.11], $p=0.02$, Fig. 3). Subgroup analysis of successful recanalization according to the study design showed that the observational studies (1.07, 95% CI [1.04 to 1.10]) but not the RCTs (1.04, 95% CI [1.00 to 1.09]) had statistically significant pooled RR in favor of the IVT + MT group.

Favorable functional outcome (or functional independence)

The pooled RR of favorable functional outcome favoured the IVT + MT group (45.2% vs. 39%; RR 1.21, 95% CI [1.13 to 1.29], $p=0.00001$, Fig. 3). The pooled studies were not homogenous ($p=0.0001$; $I^2=52\%$). Subgroup analysis of favorable functional outcome according to the study design showed that the observational studies (1.25, 95% CI [1.17 to 1.34]) but not the RCTs (0.99, 95% CI [0.89 to 1.09]) had

Fig. 1 PRISMA flow diagram of the study selection process

statistically significant pooled RR in favor of the IVT + MT group.

Improvement in NIHSS score

The overall mean difference (MD) of improvement in the NIHSS score from baseline did not favor either groups (MD − 0.34, 95% CI [− 0.80 to 0.11]). Subgroup analysis, according to the time point at which NIHSS score improvement was assessed, did not show any difference between the two groups either at 24 h (MD − 0.45, 95% CI [− 1.04 to 0.13]) or at discharge (MD − 0.70, 95% CI [− 1.51 to 0.11], Fig. 4). The pooled studies were homogenous ($p = 0.0005$, $I^2 = 65\%$). Subgroup analysis of the improvement in NIHSS score according to the study design showed that the observational studies (MD − 0.87, 95% CI [− 1.83 to 0.09]) but not the RCTs (MD − 0.15, 95% CI [− 1.71 to 1.41]) had statistically significant pooled MD in favor of the IVT + MT group (Fig. 4).

Complications

Symptomatic intracerebral hemorrhage

The pooled RR of sICH did not favor either of groups (RR 1.00, 95% CI [0.74 to 1.36], $p = 0.99$, Fig. 5). The pooled studies were homogenous ($p = 0.95$, $I^2 = 0\%$).

Symptomatic intracranial hemorrhage

The pooled RR of symptomatic intracranial hemorrhage did not favor either of groups (RR 0.88, 95% CI [0.70 to 1.10], $p = 0.27$, Fig. 5). The pooled studies were homogenous ($p = 0.20$, $I^2 = 21\%$).

Any intracranial hemorrhage

The pooled RR of symptomatic intracranial hemorrhage did not favor either of groups (RR 1.13, 95% CI [0.97 to 1.32],

Table 1 Summary of included studies

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Machado 2021 [18]	Portugal	Retrospective study	524	January 2016	December 2018	LVO within the anterior circulation including internal carotid artery (ICA), M1, M2, or M3 segment of middle cerebral artery (MCA), or anterior cerebral artery (ACA)	-No significant difference between MT + IVT and MT alone in the 90-day mRS score ($p = 0.759$) -No significant difference in the death rate at 90 days between MT + IVT and MT alone groups (17.9% vs. 23.2%; $p = 0.149$) respectively
Maier 2017 [19]	Germany	Retrospective study	109	January 2014	November 2015	LVO within the anterior and posterior cerebral circulation	-No significant difference between MT + IVT group and MT alone group in groin-to-reperfusion time (54 vs. 50 min; $p = 0.657$) -Higher reperfusion rate in MT + IVT group (69 vs. 15 patients in MT alone group, $p = 0.099$) -Better improvement in the NIHSS score during hospitalization in MT + IVT group with mean values of 8 points (SD ± 8) vs. 2 points (SD ± 7) for the MT alone group, ($p = 0.001$) -Significantly higher rate of mRS 0–2 in the MT + IVT group at discharge (34 vs. 5; $p = 0.024$)
Dimaria 2018 [20]	France	Retrospective study	1507	December 2012	December 2016	MCA (M1 or M2), terminal carotid (carotid T), or tandem occlusion (defined as extracranial ICA occlusion associated with intracranial artery occlusion)	-53.6% of IVT + MT group versus 41.8% of MT alone group showed favorable outcomes (mRS 0 to 2) -Significant difference in excellent outcome (mRS 0 to 1) and successful reperfusion in the favor of MT + IVT -No differences in intracerebral hemorrhage or 90-day mortality rates
Merlino 2017 [12]	Italy	Prospective study	66	January 2015	March 2016	LVO within the anterior or posterior circulation including ICA, M1/M2 segments of MCA, tandem or vertebrobasilar occlusion	-MT + IVT significantly improved short and long-term outcomes of the patients -The MT + IVT group showed significantly higher rate of favorable outcome (mRS score ≤ 2) at 90 days (51.5 vs. 18.2%; $p = 0.004$) and one year after the stroke (51.5 vs. 15.2%; $p = 0.002$) -MT alone patients were 6 times more likely to die than IVT + MT group during the 1-year follow up
Minnerup 2016 [13]	Germany France	Prospective study	2650	April 2012	August 2013	Not specified - All patients of AIS including occlusion of ICA, MCA (M1/M2), posterior circulation or other vessels	-The MT + IVT group showed better functional outcomes -MT + IVT yielded lower mortality rate compared with IVT alone (15% vs. 33%; $p < 0.0001$)

Table 1 (continued)

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Pienimaki 2021 [21]	Finland	Retrospective study	106	October 2016	October 2019	LVO of the anterior circulation (from ICA up to the M3 segment of the MCA)	- 90-day mRS score (0–1) was three times higher in the MT alone group ($p=0.009$) -The MT alone group showed better overall 3-month clinical outcomes than MT + IVT -No significant difference was observed between both groups in terms of process times, number of hemorrhagic complications, or modified treatment in cerebral infarction (mTICI) score
Rossi 2021 [22]	Ireland Greece Sweden Hungary	Prospective study	550	March 2017	March 2019	LVO in the anterior or posterior circulation: MCA (M1, M2, M3 or multiple segments/branches), ICA, posterior cerebral artery (PCA), ACA, common carotid artery, or vertebral/basilar occlusion	-MT + IVT significantly produced smaller clot area than MT alone (H1 = 10.155; $p=0.001$). However, the smaller clot area did not affect revascularization outcome -There was no significant difference between MT + IVT and MT alone in the number of passes for clot removal or in final mTICI score
Sallustio 2018 [23]	Italy	Retrospective study	325	August 2009	June 2017	LVO within the anterior circulation (proximal occlusion of MCA, ACA, terminal or proximal ICA in combination to an intracranial vessel)	-No significant difference between the two groups in safety and efficacy outcomes including: the rate of successful reperfusion, symptomatic intracranial hemorrhage, and 90-day functional independence -Multivariable analysis showed no difference between the 2 groups in the mortality rates, although mortality was lower in the MT + IVT group before the analysis -Onset-to-reperfusion time was longer in MT alone group (300 [90–845] vs. 288 [141–435]; $p=0.008$)
Suzuki 2021 [24]	Japan	Randomized, open-label, clinical trial	204	January 1, 2017	July 31, 2019	LVO (ICA or M1 of middle MCA)	-Favorable outcome occurred in 59.4% of patients underwent MT alone and 57.3% of MT + IVT group, with no significant difference between the two groups -90-days mortality was not significantly different between the two groups -Any intracerebral hemorrhage was observed less frequently in the MT alone group than in MT + IVT group ($p=0.02$) -Symptomatic intracerebral hemorrhage was not significantly different between the two groups ($p=0.78$)
Tajima 2019 [25]	Japan	Retrospective study	100	July 2014	November 2017	ICA or M1/M2 of MCA	-MT + IVT group showed better rate of complete recanalization (67.6% vs. 43.9%; $p=.041$) -73.5% of MT + IVT group achieved favorable outcomes (3-month mRS score ≤ 2), while 51.5% of MT group had favorable outcomes ($p=.028$)

Table 1 (continued)

Study ID	Country	Study design	*N*	From	To	Occluded vessel	Main findings
Wang 2017 [26]	China	Retrospective study	276	January 2014	June 2016	Proximal LVO within the anterior circulation including ICA, the M1/M2 segment of MCA and the A1 segment of ACA	-No significant difference between the two groups in terms of good functional outcome -Rates of mortality and symptomatic intracranial hemorrhage within 90 days were not significantly different between both groups (*p* values = 0.88 and 1 respectively) -Patients of MT alone significantly had a higher rate of successful reperfusion and a lower rate of asymptomatic intracranial hemorrhage
Weber 2017 [27]	Germany	Retrospective study	283	June 2012	August 2013	Multiple occlusion sites [ICA, carotid T, M1/M2 segments of MCA, the A1 segment of the ACA, P1 segment of PCA, or the vertebral artery (VA)]	-MT alone group and MT + IVT showed no significant differences in terms of successful recanalization rates, complication rates, and long-term favorable outcome (mRS 0–2) -48.2% of patients underwent MT alone who were eligible for IVT achieved a favorable outcome -32% of patients underwent MT alone and with absolute contraindications to IVT showed favorable outcomes and MT was safe for them
Wee 2017 [28]	Australia	Retrospective study	50	October 2013	April 2016	LVO within anterior circulation: ICA, the M1/M2 segments of MCA and Tandem extracranial occlusion	-47.6% of MT + IVT group and 51.7% of MT alone group showed neurological improvement at 24 h ($p = 0.774$) -Both groups had similar adverse events -Inpatient mortality was 20% for MT + IVT and 7.1% for MT alone ($p = 0.184$) -Intracranial hemorrhage was 14.3% in MT + IVT group and 20.7% in MT alone patients
Yang 2020 [15]	China	Multicenter, randomized, open-label trial	656	February 23, 2018	July 2, 2019	-The intracranial segment of ICA -The intracranial segment of the first or proximal second segment of MCA	-MT + IVT achieved higher percentage of successful reperfusion before thrombectomy (7.0% vs. 2.4%) and more overall successful reperfusion (84.5% vs. 79.4%) -90-day mortality was 17.7% in MT alone group and 18.8% in MT + IVT group

Table 1 (continued)

Study ID	Country	Study design	*N*	From	To	Occluded vessel	Main findings
Yi 2018 [29]	China	Retrospective study	93	January 2015	January 2017	LVO within the anterior circulation: ICA and M1 segment of MCA (proximal and distal)	-MT + IVT achieved higher successful revascularization rate than MT alone (81.1% versus 51.8%, $p = 0.004$), within shorter procedure time (59 ± 34 min vs. 94 ± 56 min, $p < 0.001$) -Compared to MT alone, MT + IVT used fewer passes of the stent retriever (1.8 ± 1.1 vs. 2.5 ± 1.4, p0.012 =ج), and achieved better prognosis (70.3% vs. 48.2%, $p = 0.035$) -Embolic complication rate was lower in MT + IVT group (18.9% vs. 39.3%, $p = 0.038$) -Both groups had similar mortality (13.5% versus 21.4%, $p = 0.334$) and similar intracranial hemorrhage symptoms (2.7% versus 12.5%, $p = 0.204$)
Zi 2021 [30]	China	Multicenter, randomized, open-label, clinical trial	234	May 20, 2018	May 2, 2020	The intracranial internal carotid artery or the first segment of MCA	-54.3% of MT alone group and 46.6% of MT + IVT group achieved functional independence (mRs 0–2) at the 90-day follow-up -No significant difference was found between the two groups in symptomatic intracerebral hemorrhage and 90-day mortality
Al-Khaled 2018 [31]	Germany	Prospective observational study	236	2011	2018	Distal ICA or MCA (M1)	-Endovascular treatment (ET) combined with IV rt-PA can be associated with decreasing levels of in-hospital mortality (9% vs. 19.6%, $p = .019$) and symptomatic intracranial hemorrhage (sICH) (2.1% vs. 8.7%, $p = .019$) when compared to ET only -The combined treatment was also associated with more favorable functional outcomes -After the adjusted logistic regression analysis was conducted, the combined treatment was associated with higher odds of achieving favorable functional outcome -No statistically significant difference was found between the 2 groups in symptomatic intracerebral hemorrhage or in-hospital mortality

Table 1 (continued)

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Balodis 2018 [8]	UK	Prospective observational study	146	Feb-14	–	ICA, MCA (M1), or both	-The combined treatment (compared to ET only) did not have any statistically significant effect on procedure time ($p=0.71$) or number of attempts ($p=0.63$) -No significant difference was found in functional independence rates or mortality rates between the two groups -Recanalization was mostly successful in both groups but slightly higher in the combined treatment group (94% vs. 89%, $p=0.4$) -The combined treatment showed higher levels pf bleeding, but it was statistically insignificant (27.32% vs. 12.19%, $p=0.09$)
Behme 2016 [32]	Germany	Retrospective study	93	Jul-12	–	MCA	-The results showed significant increase in the rates of the successful recanalization in the combined treatment group compared to the MT only group (77% vs. 44%, $p=.01$)
Broocks 2021 [33]	Germany	Prospective observational study	56	Aug-17	–	ICA or MCA (M1)	-There was no statistically significant difference in peripheral embolism between groups of direct MT and MT + IV alteplase (mean: 12.1, 95% CI 8.6–15.5 vs. 11.1, 95% CI 7.0–15.1; $p=0.701$)
Casetta 2019 [10]	Italy	Retrospective case control study	1148	–	–	IICA or MCA (M1 or M2)	-The combined treatment group had better outcome concerning the mRS score after 90 days -Multivariate analyses on binary outcome suggests that the MT + IVT group had higher probability to attain a score between 0 and 3 in mRS and lower mortality rate
Chalos 2019 [11]	Netherlands	Retrospective study	1485	Mar-14	Jun-16	ICA [ICA/ICA-T], MCA [M1/M2], ACA [A1/A2]	-Multivariable regression showed that the combined treatment group (compared to ET alone) was associated with better functional outcome and lower number of fatalities -The rates of sICH, successful perfusion and first pass effect were not different between the two groups
Charbonnier 2020 [34]	France	Retrospective study	106	January 2015	December 2016	Not specified	-The time of revascularization in the patients receiving MT only wasn't different from the time in the MT + IVT group (73 vs. 69 min, respectively; $p=0.36$) -In the successful revascularization subgroup, there was no significant difference in revascularization time between the 2 treatments, the MT only group had higher probability to score mTICI 3 than the combined treatment group, but this difference wasn't statistically significant (47 vs. 21%; $p=0.056$)

Table 1 (continued)

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Choi 2018 [35]	Korea	Prospective observational study	81	Jan-09	Jun-17	Not specified	-There was no statistically significant difference between the patients receiving MT only and the patients receiving MT + IVT regarding onset to groin puncture time (221.6 ± 110.5 vs. 204.7 ± 63.7 min, $p = 0.472$), successful reperfusion rate (60.5% vs. 58.1%, $p = 0.827$), mortality rate (18.4% vs. 9.3%, $p = 0.332$), rate of sICH (5.3% vs. 4.6%, $p = 1.000$) or favorable functional outcome (mRS 0–2) (36.8% vs. 51.2%, $p = 0.263$)
Gamba 2019 [36]	Italy	Retrospective study	145	Jan-14	Jan-17	Intracranial ICA or MCA (M1 or M2)	-The study showed that patients that received combined treatment has higher rates of functional independence at 3 months (mRS score 0–1: 48.5% vs. 18.6%; $p < 0.001$. mRS score 0–2: 67.1% vs. 37.3%; $p < 0.001$) compared to patients treated with ET only -No significant difference in mortality rates and ICH rates was found between the two groups
Guedin 2015 [37]	France	Retrospective study	68	Jan-11	Jun-13	ICA or proximal MCA	-The combined treatment group showed significantly shorter median groin puncture to recanalization time than MT group (35 min [21–60] vs. 60 min [25–91]; P 5.043) -The number of passes tended to be lower in the IVT + MT group than in the MT only group (0.08) -The combined treatment also had a higher rate of recanalization (96.4% vs. 72.5%, $p = 0.011$) and more favorable outcomes ($p = 0.21$)
Rocha 2019 [38]	Portugal	Retrospective study	234	Jan-15	Jun-17	ICA or MCA (M1 or proximal M2)	-There was no statistically significant difference between the combined treatment group and the MT only group regarding favorable functional outcome (mRS < 2) (64.9% vs. 52.5%, $p = .066$), symptomatic intracranial hemorrhage (3.3% vs. 4.9%, $p = .723$) or mortality rate (9.9% vs. 17.5%, $p = .099$)
Heiferman 2017 [39]	USA	Prospective observational study	40	Jan-15	Mar-16	ICA, MCA, or posterior circulation	-The combined treatment group failed to show any statistically significant difference compared to the MT alone group regarding hemorrhage (symptomatic: 8% vs. 4%, any: 25% vs. 11%), -successful recanalization, favorable outcome, and mortality

Table 1 (continued)

Study ID	Country	Study design	*N*	From	To	Occluded vessel	Main findings
Imbarrato 2018 [40]	USA	Retrospective study	46	2011	2015	ICA or MCA (M1)	-The MT alone group had higher rates of successful recanalization when compared to the MT alone group (86% vs. 82%, $p < 0.0001$) -The MT group also achieved higher rates of favorable outcomes (MRS < 2) (43.4% vs. 39.1%, $p = 0.8$)
Jian 2021 [9]	China	Prospective observational study	482	Nov-17	Mar-19	ICA, VA, basilar artery (BA), MCA (M1 or M2), or ACA (A1 or A2 segments)	-The study showed no difference between the patients receiving direct MT and the patients receiving the bridging therapy regarding 90 days functional outcome (MRS) -The direct MT group had shorter symptoms to groin puncture time (225 vs. 255, $p = 0.002$) and lower rates of type 2 parenchymal hemorrhage in a 24-h period (2.8 vs. 6.63, $p = 0.025$) -Also, the MT group tended to be lower in frequency of sICH (5.67% vs. 10.06%, $p = 0.061$), procedural complications (7.12% vs. 12.30%, $p = 0.052$) and distal embolies (4.07% vs. 6.95%, $p = 0.093$)
Kaesmacher 2018 [41]	Germany	Retrospective study	239	Jan-07	Jul-15	MCA	-The MT + IVT therapy (when compared to MT alone therapy) proved higher rate of successful recanalization (86.9% vs. 75.7%, $p = 0.028$) -However, most of the effects of the MT + IVT therapy were observable only in distal MCA occlusions and not in proximal -In distal MCA occlusions, the combined therapy had higher rates of successful recanalization and strong neurological improvement
Abilleira 2017 [42]	Spain	Retrospective study	1166	Jan-11	Oct-15	MCA, ICA, or tandem lesion	-There was no significant difference between the two groups (IVT alone, IVT + EVT) regarding mortality (OR, 1.07; 95% CI, 0.74–1.54) symptomatic bleeding (OR 0.56; 95%CI,0.25–1.27) or better outcomes (OR 0.97; 95% CI, 0.74–1.27)
Bhatia 2012 [43]	Canada	Retrospective study	419	2002	2009	BA, VA, M1 and M2 segments of MCA, T or L type occlusions of ICA	-Mortality and favorable outcomes didn't show a significant difference between the 2 groups
Broeg-morvay 2016 [7]	Switzerland	Retrospective study	422	Feb-09	Aug-14	ICA, M1, M2 segments of MCA	-Functional independence, mortality and intracerebral hemorrhage rates didn't differ from the 2 groups
Davalos 2012 [44]	Switzerland, Spain, Germany, France, Sweden	Retrospective study	141	start of June 2010	end of June 2010	Cervical and terminus ICA, M1 and M2 segments of MCA, VA, BA, PCA, superior cerebellar artery	-Good outcome was achieved more in the combined treatment group (66% vs. 42%; $p = 0.01$)

Table 1 (continued)

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Kass-hout 2014 [45]	USA	Retrospective study	104	2005	2010	ACA, ICA, MCA, posterior circulation	-Statistical analysis failed to show a statistically significant difference between bridging therapy and endovascular therapy alone regarding good functional outcomes (37.5% and 32.76%; P [0.643]), mortality rate (19.04% and 29.03%; $p=0.5618$) and symptomatic intracerebral hemorrhage (11.9% and 9.68%; P [0.734]). However, a statistically significant difference was established in the time from onset to treatment (227 + or − 88 min vs. 125 + or – 40 min; $p<0.0001$)
Leker 2015 [16]	Israel	Prospective study	57	Nov-10	Oct-14	M1 segment of MCA	-Bridging did not impact mortality rate (87.5% vs. 90%) or the chances of favorable outcome ($p=0.87$)
Pfefferkorn 2011 [46]	Germany	Prospective study	65	Jan-03	Jun-06	M1 segment of MCA, carotid T, and BA	-Combined therapy achieved higher levels of good functional outcomes (p < 0.05) and achieved shorter intervention time (when successful recanalization was done) (24.8 + or- 22.8 vs. 44.2 + or- 40.5 min; $p=0.05$)
Rai 2017 [47]	USA	Prospective study	90	2013	2016	Carotid T and MCA	-There was no significant difference between the 2 groups regarding recanalization ($p=0.12$, $p=0.93$; in patients presented less than 4.5 h and more than 4.5 h respectively), favorable outcomes ($p=0.45$, $p=0.75$), hemorrhage ($p=0.46$, 0.78), mortality rate ($p=0.07$, $p=0.33$) or home discharge ($p=0.45$, $p=0.27$)
Li Gong 2019 [48]	USA	Retrospective study	73	December 2015	2018	MCA	-There are no differences in the functional outcome, mortality, and intracerebral hemorrhage. In the histological clot analysis, the cardioembolic clots without intravenous thrombolysis pretreatment had higher RBC ($p=0.042$) and lower fibrin ($p=0.042$) percentages than the large-artery atherosclerosis thrombi. Similar findings were observed in the thrombi treated with recombinant tissue plasminogen activator ($p=0.012$). In conclusion, there was no difference in the functional outcomes between the direct MT and bridging therapy groups

Table 1 (continued)

Study ID	Country	Study design	N	From	To	Occluded vessel	Main findings
Alonso de Leciñana M 2017 [49]	Spain	Prospective study	131	2012	2015	MCA, PCA, and ICA	-Of 131 patients, 21 (16%) had medical contraindications for IVT and were treated primarily with MT, whereas 110 (84%) underwent IVT, followed by MT in 53 cases (40%). The recanalization rate and procedural complications were similar in the two groups. There were no SICHs after primary MT vs. 3 (6%) after IVT + MT. Nine patients (43%) in the primary MT group achieved independence (mRS 0–2) compared with 36 (68%) in the IVT + MT group ($p = 0.046$). Mortality rates in the two groups were 14% ($n = 3$) vs. 4% ($n = 2$) ($p = 0.13$). Adjusted ORs for independence in patients receiving standard IVT + MT vs. MT in patients with medical contraindications for IVT were 2.8 (95% CI 0.99 to 7.98) and 0.24 (95% CI 0.04 to 1.52) for mortality
Bourcier R 2018 [50]	France	Retrospective study	141	2014	2016	ICA, MCA, and ACA	-There was a significant difference between IVT + MT and MT groups in the median time between imaging and groin puncture (median 97 min vs. 75, $p = 0.007$), the rate of ICH (44% vs. 27%, $p = 0.05$), but not for symptomatic ICH (18% vs. 13%, $p = 0.49$). There was a trend toward a higher rate of ICH (OR = 2.3, 95% CI 0.9 to 5.9, $p = 0.09$) in the BT group compared with the MT alone group, with no difference in mRS score ≤ 2 at 3 months (OR = 1.6, 95% CI 0.7 to 3.7, $p = 0.29$)
Ferrigno M 2018 [51]	France	Prospective study	485	2012	2017	MCA and ICA	-In MT group, 22% of patients had a favorable outcome versus 35% in IVT/MT group (adjusted relative risk, 1.76; 95% confidence interval, 1.23–2.55). Mortality within 3 months occurred less frequently in IVT/MT group (14% versus 32%; adjusted relative risk, 0.46; 95% confidence interval, 0.31–0.70). Successful reperfusion (Thrombolysis in Cerebral Infarction scale 2b-3) was more frequent in IVT + MT group (75% versus 60%; adjusted relative risk, 1.30; 95% confidence interval, 1.11–1.53). There was no difference between groups on hemorrhagic complications

Table 1 (continued)

Study ID	Country	Study design	*N*	From	To	Occluded vessel	Main findings
Maingard J 2019 [52]	Ireland	Retrospective study	355	2010	2016	Any LVO	-Higher reperfusion rate in the MT + IVT group (unadjusted odds ratio (OR) 2.2, 95% confidence interval (CI): 1.29–3.73, $p=0.004$) -This effect was attenuated when all variables were considered (adjusted OR (AOR) 1.22, 95% CI: 0.60–2.5, $p=0.580$) -Higher rate of functional independence (90-day mRS 0–2) in the IVT + MT group (AOR 2.17, 95% CI: 1.06–4.44, $p=0.033$) -No significant difference in major complications -Fewer thrombectomy passes (2 vs. 3, $p=0.012$) were required to achieve successful reperfusion in the IVT + MT group
Park 2017 [53]	Korea	Retrospective cohort	639	2008	2013	–	-IVT + MT group achieved higher rate of successful recanalization (1.96 [1.23–3.11]) and reduced 90-day mortality (0.58 [0.35–0.97]) but not with symptomatic hemorrhagic transformation (SHT) (0.96 [0.48–1.93])
LeCouffe 2021 [54]	Netherlands, Belgium and France	Randomized controlled trial	539	24 January 2018	28 October 2020	Intracranial ICA, carotid T, M1, proximal M2 segments of MCA, tandem lesion	-No significant difference between the two groups regarding mRS median score ($p=0.28$), mortality (OR = 1.39, CI = 0.84–2.3), symptomatic intracerebral hemorrhage (OR = 1.3, CI = 0.6–2.81) or any intracranial (OR = 0.97, CI = 0.68–1.38)
Goyal 2018 [55]	USA	Retrospective study	583	May 2013	May 2015	Any LVO	-The IVT + MT group had greater functional improvement than MT alone group ($p=0.037$) at 90 days
Tong 2021 [56]	China	Retrospective study	1026	November 2017	March 2019	ICA, MCA (M1/M2), ACA (A1/A2), vertebrobasilar artery, and PCA (P1)	-No significant differences were detected between the two groups in the successful recanalization (86.6% versus 89.3%; $p=0.23$) and 90-day mRS -MT group had a lower rate of symptomatic intracranial hemorrhage (5.5% vs. 10.1%), shorter door-to-puncture time (median, 112 vs. 136 min), and lower rates of embolization (4.6% vs. 8.1) than the MT + IVT group
Kandregula 2021 [57]	USA	Retrospective study	2895	2017	2018	MCA	-The MT + IVT group had minimal rate of disability in comparison with the MT group (23.8% versus 18.2% -Decreased risk of progressing to severe disability from minimal disability in the IVT + MT group

Table 2 Baseline characteristics of the included studies' populations

Study ID	Age Mean (SD)		Sex (male) (N, %)		Past stoke (N, %)		Past cardiovascular disease		NIHSS at baseline median (IQR)		Onset to groin time	
	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT
Al-Khaled 2018 [31]	69 (13)	68.7 (14)	62 (43)	46 (50)	36 (26)	32 (36)	101	71	13 (10–17)	13 (10–17)	88 (55–103)	83 (60–103)
Balodis 2019 [8]	72 (12.5)	72 (9.9)	38	28	–	–	–	–	15 (12–18)	16.5 (14–20)	260 (240–320)	280 (240–347)
Behme 2016 [32]	74 (32–91)	74 (48–91)	34	9	–	–	–	–	16 ± 6	17 ± 8	194 (83–396)	192 (72–329)
Broocks 2021 [33]	71.5 (66.75–81)	71 (62–82.25)	16	14	–	–	12	20	12.5 (10–17)	14 (9.75–16.25)	–	–
Casetta 2019 [10]	67.6	68.8	313	251	17	34	417	402	18 (14–21)	18 (14–22)	120 (80–165)	96 (68.6–140)
Chalos 2019 [11]	70 (59–79)	72 (63–80)	621	171	164	83	562	180	16 (11–20)	17 (13–20)	206 (160–260)	215 (158–294)
Charbonnier 2020 [34]	67	74	44	8	–	–	–	–	18	19	290	298
Choi 2018 [35]	68.9 ± 12.8	72.6 ± 14.1	29	17	5	8	29	25	13 (10–16)	15 (11–17)	204.7 ± 63.7	221.6 ± 110.5
Gamba 2019 [36]	71.9 (10.6)	69.1 (13.2)	38	37	–	–	52	53	18 (15–21)	19 (15–20)	–	–
Guedin 2015 [37]	69.2 (13.5)	64.6 (15.3)	11	15	–	–	11	17	18 (13–19)	15 (10–20)	240 (187–275)	204 (175–290)
Rocha 2018 [38]	70.90 (12.60)	71.93 (13.67)	70	39	–	–	104	54	16.28 (4.98)	15.67 (4.48)	245	267.5
Heiferman 2017 [39]	67 (56–74)	69 (63–78)	10	5	–	–	–	–	20 (15–25)	18 (14–22)	300 (244–375)	293 (272–368)
Imbarrato 2018 [40]	69.2 (± 14.7)	71.1 (± 16.2)	–	–	–	–	–	–	16.6	17.6	–	–
Jian 2021 [9]	72 (68–78)	73 (69–78)	87	172	–	–	115	194	17 (13–21)	18 (13–23)	–	–
Merlino 2017 [12]	69.6 (12.7)	70.8 (12.2)	18 (54.5)	14 (42.4)	3 (9.1)	3 (9.1)	16 (48.5) 26 (78.8) #	19 (57.6) ǂ 21 (63.6) #	17.5 (14–20)	20 (14–23)	–	–
Minnerup 2016 [13]	68.3 (13.7)	68.7 (14.7)	304 (50.4)	242 (48)	77 (12.8)	104 (20.6)	461 (76.5) # 225 (37.3) ǂ 123 (20.4)Ŧ	382 (75.8) # 231 (45.8) ǂ 126 (25.0) Ŧ	15.0 (7.0)	15.0 (9.0)	–	–
Pienimaki 2020 [21]	69 (12)	72 (11)	37 (64)	30 (62)	–	–	29 (50) # 37 (64) ǂ	31 (65) # 19 (40) ǂ	16.5 (8)	14 (9)	–	–
Rossi 2020 [22]	–	–	–	–	–	–	–	–	17[12–21]	16[11–20]	–	–
Sallustio 2018 [23]	71.8 (14.2)	70.3 (12.9)	82 (42.5)	58 (44)	–	–	145 (75) # 84 (44) ǂ	89 (67) # 68 (52) ǂ	19 (2–26)	19 (3–25)	225 (77–380)	222.5 (70–809)

Table 2 (continued)

Study ID	Age Mean (SD)		Sex (male) (*N*, %)		Past stoke (*N*, %)		Past cardiovascular disease		NIHSS at baseline median (IQR)		Onset to groin time	
	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT
Suzuki 2021 [24]	76 (67–80)	74 (67–80)	72 (70)	56 (55)	14 (14)	12 (12)	61 (59) # 64 (62) ǂ	61 (60) # 57 (56) ǂ	17 (12–22)	19 (13–23)	–	–
Tajima 2019 [25]	74.3 (8.6)	75.7 (10.6)	22 (64.7)	38 (57.6)	5 (14.7)	17 (25.8)	15 (44.1) # 18 (52.9) ǂ	40 (60.6) # 41 (62.1) ǂ	19.8 ± 4.1	19.6 ± 6.2	–	–
Wang 2017 [26]	67 (58.75–73)	67 (58.75–75)	78 (56.5)	76 (55.1)	16 (11.6)	15 (10.9)	–	–	17 (13–21.25)	16 (13–21)	–	–
Weber 2016 [27]	70.2 (12.6)	69.3 (14.9)	52 (49.5)	78 (53.8)	13 (12.9)	34 (23.8)	82 (79.6) # 26 (25.5) ǂ	104 (71.7) # 56 (38.9) ǂ	15.5 (12–20)	15 (9–19)	–	–
Wee 2017 [28]	73 (16)	71 (14)	8 (38)	16 (55)	5 (23.8)	3 (10.3)	13 (61.9) # 9 (42.9) ǂ	21 (72.4) # 17 (58.6) ǂ	15 (5)	15 (7)	-	-
Yang 2020 [15]	69 (61–76)	69 (61–76)	181 (55.0)	189 (57.8)	47 (14.3)	43 (13.1)	149 (45.3) ǂ 201 (61.1) #	152 (46.5) ǂ 193 (59.0) #	17 (14–22)	17 (12–21)	–	–
Yi 2018 [29]	66 (13)	65 (11)	17 (45.9)	30 (53.6)	–	–	19 (51.4) # 19 (51.4) ǂ	22 (39.3) # 35 (63.6) ǂ	18 (11–23)	18 (10–28)	–	–
Zi 2021 [30]	70 (60–78)	70 (60–77)	66 (55.9)	66 (56.9)	19 (16.1)	14 (12.1)	74 (62.7) # 62 (52.5) ǂ	69 (59.5) # 62 (53.5) ǂ	16 (13–20)	16(12–20)	210 (179–255)	200 (155–247)
Leker 2015 [16]	66.8 (13.7)	64.4 (66)	8 (33)	15 (45)	2 (8)	7 (21)	10 (42)	18 (54)	19.5	20	–	–
Abilleira S 2017 [42]	68.6 (12.8)	68.1 (13.5)	306(54)	309 (51.6)	44 (8.1)	87 (14.5)	–	–	17 (13–20)	17 (12–20)	–	–
Rai 2017 [47]	63 (19)	69 (18)	20(39)	20 (53)	–	–	24 (46)	10 (26)	18 (13–23)	16 (10–22)	–	–
Kass-Hout T, 2014 [45]	67.64 (14.85)	69.26 (15.76)	20 (47.6)	29 (46.8)	14 (33.33) ǂ – 32 (76.19) #	-24 (38.71) ǂ – 42 (67.74) #	–	–	14.78 (4.7)	16 (5.37)	–	–
Bhatia 2014 [43]	63 (15)	60 (14)	50%	55%	18%	15%	–	–	17 (9)	16 (10)	226·5 (102)	267 (601·5)
Davalos 2012 [44]	66.2 (12.7)	66.4 (13.6)	45 (61)	34 (51)	–	–	–	–	17 (11, 21)	18 (15–20)	–	–
Pfefferkorn T2012 [46]	62.1(14.4)	64.6 (12.9)	16 (62)	9 (39)	19 (7.1)	19.6 (6)	–	–	–	–	–	–
Gong L2019 [48]	69 (9)	71 (10)	27	15	–	–	(20/42) ǂ	(27/31)ǂ	13 (6–21)	15 (6–22)	–	–
Goyal 2018 [55]	62.5 ± 17.0	61.0 ± 19.8	47.6%	52.7%	–	–	–	–	17 (13–21)	16 (12–21)	223 (158–295)	303 (195–455)
Alonso 2017 [49]	64 (51–73)	74 (66–78)	24 (45)	9 (43)	5 (9)	3 (14)	–	–	17 (14–22)	19 (13–22)	275 (225–345)	210 (168–257
Bourcier 2017 [50]	68 (15)	73 (15)	55(65)	24(43)	–	–	–	–	18 (14–22)	18 (16–23)	240 (200–300)	200 (140–280)

Table 2 (continued)

Study ID	Age Mean (SD)		Sex (male) (*N*, %)		Past stoke (*N*, %)		Past cardiovascular disease		NIHSS at baseline median (IQR)		Onset to groin time	
	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT	With IVT	Without IVT
Ferrigno M 2018 [51]	66.3 (15.3)	66.3 (15.3)	160 (46.0	61 (44.5)	52 (14.9	43 (31.4)	–	–	16.2 (5.9)	16.1 (5.1)	–	–
Maingard J 2019 [52]	66 (14)	68 (14)	116 (55)	81 (56)	–	–	–	–	17 (5)	17 (6)	32 (30)	33 (38)
Park HK 2017 [53]	68 ± 12	69 ± 12	260 (57)	103 (57)	85 (19)	46 (25	–	–	15 (11 – 19)	15 (10 – 18.5)	–	–
N.E. LeCouffe 2021 [54]	69 (61–77)*	72 (62–80)	144 (54.1)	161 (59.0%	44 (16.5)	47 (17.2)	63 (23.7)	86 (31.5)	16 (10–20)	16 (10–20)	64 (51–78)	63 (50–78
Tong 2021 [56]	64 (55–72)	66 (55–74)	266 (62.4)	392 (65.3)	64 (15.0)	129 (21.5)	131 (30.8) ǂ 229 (53.8) #	209 (34.8) ǂ 335 (55.8) #	16 (11–20)	17 (13–22)	–	–
Kandregula 2021 [57]	69.23 (4.4)	69.9 (14.8)	563 (45.9)	765 (45.8)	–	–	488 (39.8) ǂ 828 (67.5) #	671 (40.2) ǂ 1117 (66.9) #	16.6 (5.97)	16.2 (6.1)	–	–

ǂ Number (%) of patients with atrial fibrillation

Number (%) of patients with hypertension

$p = 0.11$, Fig. 5). The pooled studies were homogenous ($p = 0.12$, $I^2 = 32\%$).

Parenchymal hematoma

The pooled RR of parenchymal hematoma did not favor either of groups (RR 1.13, 95% CI [0.82 to 1.56], $p = 0.46$, Fig. 5). The pooled studies were homogenous ($p = 0.13$, $I^2 = 35\%$).

Procedure-related complications

The pooled RR of procedure-related complications did not favor either of groups (RR 1.13, 95% CI [0.82 to 1.55], $p = 0.46$, Fig. 5). The pooled studies were homogenous ($p = 0.12$, $I^2 = 45\%$).

Time variables

The overall mean difference (MD) of the onset-to-groin time did not favor either of groups (MD − 9.11 min, 95% CI [− 26.28 to 8.06], $p = 0.30$). The overall mean difference (MD) of the procedural time did not favor either of the two groups (MD − 2.40 min, 95% CI [− 8.44 to 3.64], $p = 0.44$; forest plots are available in the supplementary file).

Results of the subgroup analysis

We conducted subgroup analysis for the main outcomes according to the study design (RCTs only vs. observational studies vs. all studies). Observational studies showed an advantage for the IVT + MT over MT alone in terms of mortality, successful recanalization (mTICI 2b-3), and 90-day favorable outcome (0–2), but RCTs did not show the same advantage (Table 3).

Results of the meta-regression analysis

We ran multiple meta-regression analysis models to test whether the type of intervention or the onset-to-groin time could significantly influence the effect estimates. Bridging therapy was a significant predictor of less mortality (ß − 0.073; $p = 0.003$) and more successful recanalization (ß 0.099; $p = 0.002$) when compared with MT alone as the reference category in the regression model (Table 4). On the other hand, the onset-to-groin time was significantly associated with symptomatic intracranial hemorrhage (ß 0.001; $p = 0.017$) or any intracranial hemorrhage (ß 0.001, $p = 0.026$, Fig. 6).

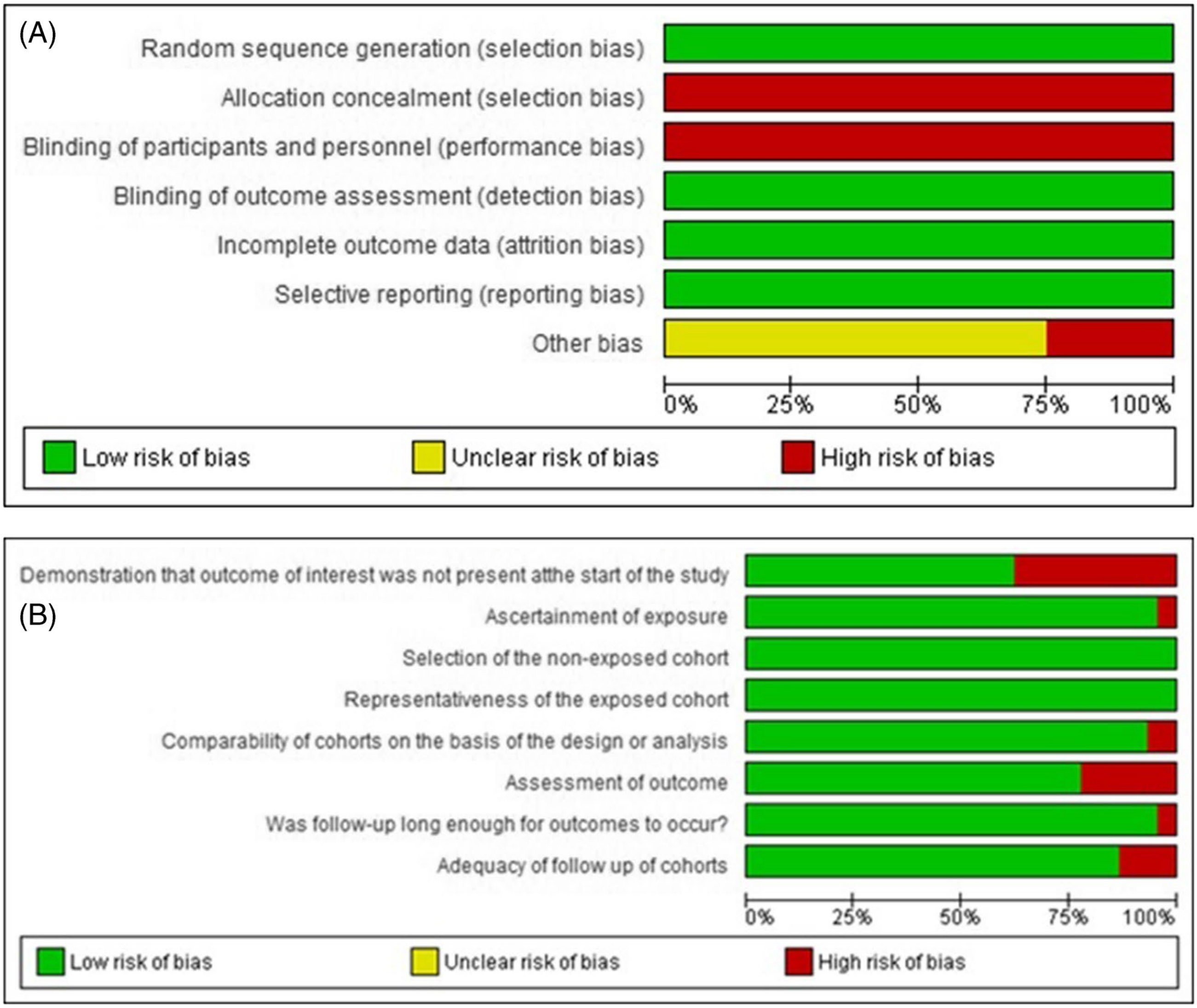

Fig. 2 Summary of the risk of bias in the included studies; **A** in randomized controlled trials and **B** in observational studies

Discussion

Summary of the main findings

The present meta-analysis provides evidence (class 1) that for patients with AIS-LVO, IVT + MT is superior to direct MT alone in terms of the rates of mortality, successful recanalization, complete recanalization, and the favorable functional outcome. Notably, our meta-analysis found that there were no significant differences between the two groups in terms of onset-to-groin time, procedural time, NIHSS scores (at 24 h and discharge), or complications including both hemorrhagic and procedure-related complications.

In terms of the improvement in NIHSS score, the subgroup analysis according to the study design showed consistent findings between RCTs and non-RCTs. However, in terms of mortality, successful recanalization (mTICI 2b-3), and 90-day favorable outcome, observational studies favoured IVT + MT over MT alone while RCTs showed no difference between the two groups (Table 3). RCTs addressing the comparisons between both treatment options are scarce; therefore, most of the evidence synthesized in this systematic review and meta-analysis is built on observational data which might be susceptible to confounding bias. Nonetheless, until further large, better-designed RCTs are conducted, the present meta-analysis provides the most comprehensive,

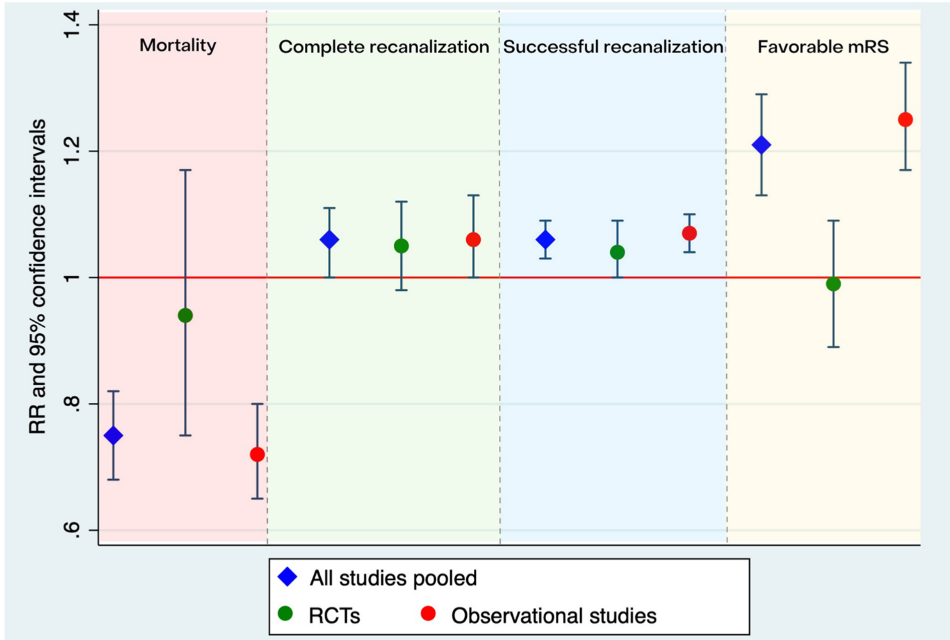

Fig. 3 Summary of the pooled RR and the corresponding 95% CI for the mortality, successful recanalization, complete recanalization, and functional independence with subgrouping according to study design

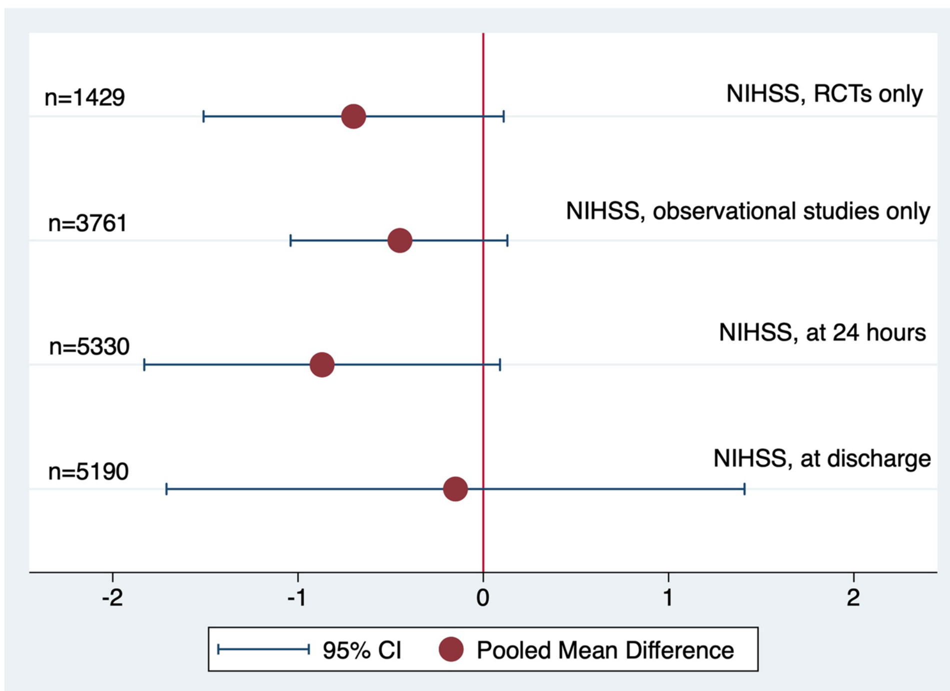

Fig. 4 Summary of the pooled MD and the corresponding 95% CI for the improvement in the NIHSS score from baseline to endpoint between the study groups with subgrouping according to time of evaluation and study design

up-to-date, evidence-based guidance on the comparison of MT + IVT versus MT alone in AIS patients. The outcomes of this meta-analysis span most of the clinically important outcomes for decision making including mortality, complete successful recanalization, functional independence on the mRS, NIHSS score, onset-to-groin time, procedural time, and procedure-related complications.

Explanation of the study findings

A few physiological mechanisms have been proposed to explain why MT + IVT might be superior to MT alone. On the one hand, it is suggested that IVT might provide synergistic effects by preparing the microvascular environment before MT. Furthermore, IVT might shorten the procedural time and reduce catheterization attempts [8]. On the other

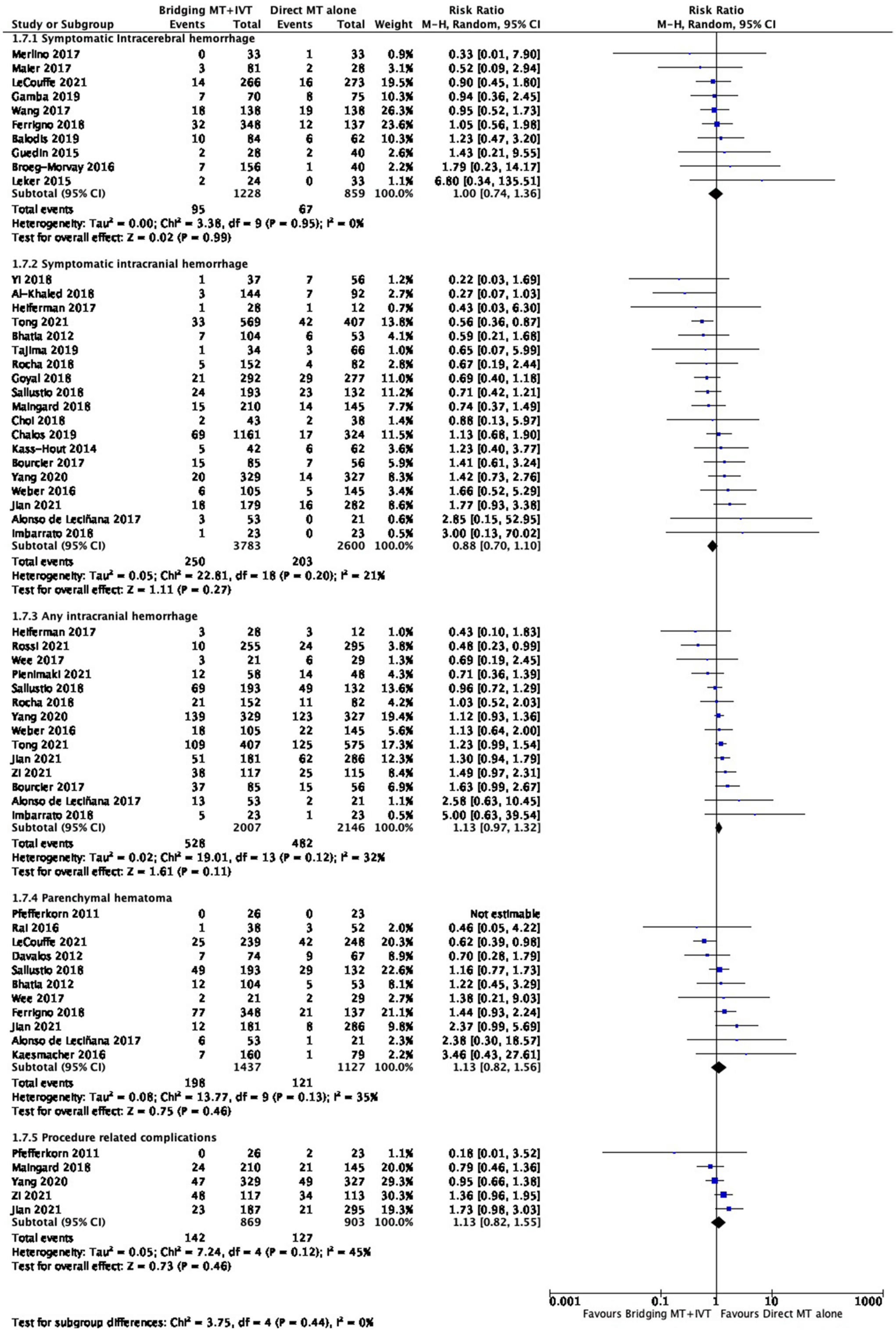

Fig. 5 Pooled RR and the corresponding 95% CI for the complications

Table 3 Summary of the subgroup analysis results, data are stratified according to the study design (RCTs only, observational studies only, and all studies)

Outcome	RCTs	Observational studies	All studies
Mortality	No difference 0.94 [0.75, 1.17]	Favors MT + IVT 0.72 [0.65, 0.80]	Favors MT + IVT group 0.75 [0.68, 0.82]
Successful recanalization (TICI 2b-3)	No difference 1.04 [1.00, 1.09]	Favors MT + IVT 1.07 [1.04, 1.10]	Favors MT + IVT group 1.06 [1.03, 1.09]
90-day favorable outcome (0–2)	No difference 0.99 [0.89, 1.09]	Favors MT + IVT 1.25 [1.17, 1.34]	Favors MT + IVT group 1.21 [1.13, 1.29]
Improvement in NIHSS score	No difference − 0.15 [− 1.71, 1.41]	No difference − 0.87 [− 1.83, 0.09]	No difference − 0.70 [− 1.51, 0.11]

Table 4 Results of the meta-regression analysis of the onset to groin time and other outcomes

Outcome variable	Intervention (MT without IVT as reference category)	Onset to groin time	*P* value
Mortality	ß − 0.073; *p* = **0.003**	ß 0.001; *p* = 0.100	**0.001**
Complete recanalization	ß 0.075; *p* = 0.453	ß 0.001; *p* = 0.547	0.684
Successful recanalization	ß 0.099; *p* = **0.002**	ß 0.001; *p* = 0.630	**0.010**
NIHSS score	ß − 1.010; *p* = 0.415	ß 0.008; *p* = 0.422	0.481
Symptomatic intracerebral hemorrhage	ß − 0.009; *p* = 0.511	ß 0.001; *p* = 0.086	0.206
Symptomatic intracranial hemorrhage	ß 0.001; *p* = 0.939	ß 0.001; *p* = **0.017**	0.057
Any intracranial hemorrhage	ß 0.075; *p* = 0.107	ß 0.001; *p* = **0.026**	**0.031**
Parenchymal hematoma	ß 0.036; *p* = 0.312	ß 0.001; *p* = 0.062	0.131

hand, IVT might facilitate the lysis of distal emboli resulting from thrombus fragmentation. Therefore, it might reduce the risk of procedural complications [15, 16].

Agreement and disagreement with previous studies

The first RCT on MT + IVT versus direct MT alone showed that direct MT was not inferior in terms of the functional outcome [15]. Additionally, the bridging therapy did not significantly reduce the numbers or the size of peripheral emboli compared with direct MT [7]. In another RCT by Broeg-Morvay et al. [7], MT + IVT did not provide additional benefits compared with MT alone in patients with no contraindications for IVT. Leker et al. [16] showed in their pilot study that patients who received IVT + MT needed fewer attempts during the EVT, while the study by Balodis et al. [8] showed that recanalization was achieved by the first pass in > 50% of cases within both groups without a significant difference.

A meta-analysis by Mistry et al. [17] examined 13 retrospective studies and found superior benefits of using bridging therapy in combination with IVT over direct MT in terms of mRS score and mortality. A summary of the results of our meta-analysis in comparison with previous meta-analyses is shown in Table 5.

Significance of the work

This study expands the literature by providing class I evidence that bridging therapy with IVT in combination with MT is superior to the direct MT without IVT for patients with AIS-LVO. A few individual studies and previous meta-analyses revealed that direct MT alone is not inferior to IVT + MT [1–3]. Moreover, some of these prior studies suggested that the combination of bridging IVT and MT might be associated with an increased risk of hemorrhagic complications [4]. However, the present meta-analysis showed a significant difference in favor of the bridging therapy. In this study, we analyzed data from 49 studies (4 RCTs and 45 non-RCTs) with a total of 36,123 patients, making it, to the best of our knowledge, the largest and most comprehensive meta-analysis addressing this comparison to date.

Strength points and limitations

This study has several strong points including: (1) We ran comprehensive research on multiple databases finding and including more studies than previously published meta-analyses, (2) We ran multiple sensitivity analyses to test the counterfactual, (3) We conducted all steps according to the guidelines of Cochrane Handbook of Systematic Reviews

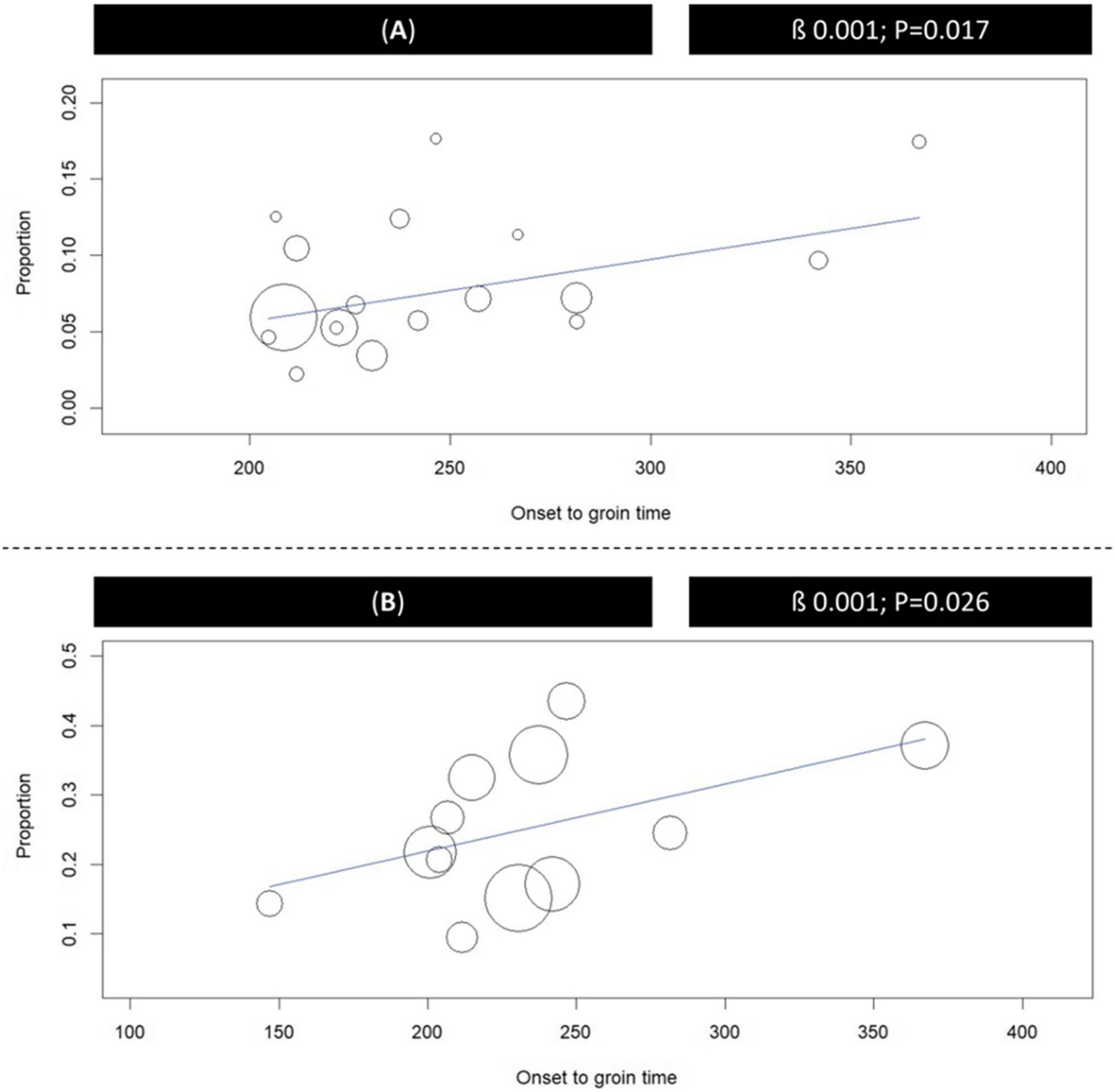

Fig. 6 Results of the meta-regression analysis (**A**) impact of onset of groin time on the incidence rate of symptomatic intracranial hemorrhage, and (**B**) impact of the onset-to-groin time on the incidence rate of any intracranial hemorrhage

and Meta-analysis of interventions, (4) This manuscript is reported according to the PRISMA statement, and (5) For all outcomes, we stratified the effect estimates by the study design into RCTs only, non-RCT studies only, and all. This allowed us to synthesize statistically robust evidence without compromising the overall quality of the review.

Nonetheless, this study has a few limitations, including (1) some studies applied pre-selection criteria for assigning patients to the bridging therapy or the direct MT groups; such pre-selection might provide an opportunity to confounding variables to influence the study outcomes. (2) Some studies included only patients for whom IVT was not contraindicated which narrows the external validity of the results; this comparison and results are not applicable in patients for whom IVT is contraindicated since direct MT will be the first-line intervention for this subgroup of patients. (3) This meta-analysis, and also the previous meta-analyses, did not take into consideration the impact of the

EVT device on such a comparison. This limitation stems from the lack of data about the used EVT technique in the included patients.

Table 5 Summary of the previous meta-analyses results

Previous meta-analyses	Number of studies	Number of patients	Favorable outcome (90-day mRS 0–2)	Successful recanalization	Any intracranial hemorrhage	Symptomatic intracranial hemorrhage
Podlasek 2021 [58]	4 RCTs	1633	No difference	Higher in the MT + IVT group	Higher in the MT + IVT group	No difference
Fan 2021 [59]	30 (4 RCTs, 26 observational)	8970	Higher in the MT + IVT group	Higher in the MT + IVT group	No difference	No difference
Vidale 2020 [60]	35 (4 RCTs, 31 observational)	9117	Higher in in the MT + IVT group	Higher in the MT + IVT group	N/A	No difference
Katsanos 2019 [61]	38 (4 RCTs, 34 observational)	11,798	Higher in in the MT + IVT group	Higher in in the MT + IVT group	No difference	No difference
Phan 2017 [62]	12 (Observational studies)	2615	No difference	No difference	No difference	No difference
Mistry 2017 [17]	13 (3 RCTs, 10 non-RCTs)	2943	Higher in in the MT + IVT group	Higher in in the MT + IVT group	N/A	No difference
Tsivgoulis 2016 [63]	3 (RCTs addressing the target comparison)	1916	No difference	N/A	N/A	N/A
Our meta-analysis	49 (4 RCTs, 45 observational studies)	36,123	Favors MT + IVT group 1.21 [1.13, 1.29]	Favors MT + IVT group 1.06 [1.03, 1.09]	No difference (RR 1.13, 95% CI 0.97 to 1.32, $p = 0.11$)	No difference (RR 0.88, 95% CI 0.70 to 1.10, $p = 0.27$)

Conclusion

For patients with AIS-LVO, IVT + MT is associated with slightly better rates of survival, successful and complete recanalization, and favorable independence as compared with the direct MT alone. The cost-effectiveness of the bridging therapy combined with MT compared with the direct MT alone should be evaluated in future studies to guide decision-making in the clinical setting. Additionally, since most of the available data are from observational studies, further clinical trials are needed to provide more robust evidence on this comparison.

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Declarations

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Hazem S. Ghaith[1,2] · Mohamed Elfil[2,3] · Mohamed Diaa Gabra[2,4] · Asmaa Ahmed Nawar[2,5] · Mohamed Sameh Abd-Alkhaleq[2,6] · Khaled M. Hamam[2,6] · Lara Ebrahim Aboelnasr[2,7] · Esraa Ayman Elgezery[2,8] · Mohamed Hosny Osman[2,5] · Hanaa Elsayed[2,5] · Sarya Swed[2,9] · Ulrick Sidney Kanmounye[2,10] · Ahmed Negida[2,5,11,12]

[1] Faculty of Medicine, Al-Azhar University, Cairo, Egypt

[2] Medical Research Group of Egypt, Cairo, Egypt

[3] Department of Neurological Sciences, University of Nebraska Medical Centre, Omaha, NE, USA

[4] Faculty of Medicine, South Valley University, Qena, Egypt

[5] Faculty of Medicine, Zagazig University, Zagazig, Egypt

[6] Faculty of Medicine, October 6 University, Giza, Egypt

[7] Faculty of Medicine, Misr University for Science and Technology, 6th October City, Egypt

[8] Faculty of Medicine, Menofia University, Menofia, Egypt

[9] Faculty of Medicine, Aleppo University, Aleppo, Syria

[10] Research Department, Association of Future African Neurosurgeons, Yaounde, Cameroon

[11] School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

[12] Department of Global Health, Harvard Medical School, Boston, MA, USA