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Direct mechanical thrombectomy versus bridging therapy in acute ischemic stroke: A systematic review and meta-analysis of randomized clinical trials

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1. Introduction

Acute ischemic stroke (AIS) is one of the leading causes of mortality and disability worldwide, with up to 50% of survivors with neurological deficits and chronic disability.[1,2] Considering time as the most important factor in its management, it is necessary to provide early revascularization interventions to limit neuronal damage and avoid poor outcomes.[3,4]

Since 2015, several randomized clinical trials (RCTs) have established the safety and efficacy of mechanical thrombectomy (MT) in patients with large vessel occlusion (LVO) of anterior cerebral circulation.[5,6] However, current clinical guidelines for early management of acute ischemic stroke recommends that intravenous thrombolysis (IVT) must be offered to all eligible patients as first-line treatment, even if MT is being considered for their management, within 4.5 h of symptom onset.[7–9]

Recent clinical trials, observational studies, as well as pooled data and meta-analyses, suggest that direct mechanical thrombectomy (dMT) could be as effective as bridging therapy (BT), obtaining good functional results on its own.[10–22] In clinical practice, IVT prior to MT (BT) has potential benefits and risks. Although some studies suggested that IVT may increase the perfusion of large occluded vessels and improve the general outcome, the recanalization rate is relatively low, especially in proximal vessel occlusions.[23,24] Moreover, it can potentially increase the risk of intracranial bleeding (ICH),[12,22,25] lead to clot fragmentation and migration, as well as complicating the patient management algorithm, particularly in centers where the "drip and ship" protocol is applied, causing delays in the initiation of MT.[26,27]

It is still unclear whether BT with prior IVT adds some benefits in patients with LVO-AIS. Previous meta-analyses found that BT was superior to dTM in terms of functional independence.[28,29] However, other authors differ as they have not found significant differences between the two groups, although they do report differences in reperfusion rates and risk of intracranial hemorrhage, favoring dMT.[20,22,30] Results between studies differ widely, so the debate continues.

We performed a systematic review and meta-analysis of completed RCTs, aiming to assess whether revascularization dMT is more effective than BT in achieving functional independence in patients with acute ischemic stroke.

2. Methods

2.1. Search strategy

This study was performed following the PRISMA guidelines and the study protocol was registered in PROSPERO (CRD42021241901). Two reviewers systematically searched electronic databases, including PubMed/MEDLINE, EMBASE, Cochrane Central, Scopus and Web of Science for clinical trials comparing the efficacy of BT to dMT. The search strategy included the combination of the following keywords:

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"ischemic stroke", "cerebrovascular disease", "thrombolysis" and "mechanical thrombectomy", as either keywords or MeSH terms. The specific search strategy in databases is reported in the supplementary material. First, the studies relevant to the investigation were stored in a database and duplicates were excluded. Two authors (MCC, GVT) reviewed titles and abstracts independently (blinded) in the Rayyan QCRI tool. Later, the selected studies were searched as full text and a second review was carried out to assess eligibility. Reference lists and citing articles of included publications were also reviewed to increase the identification of relevant studies.

3. Selection criteria

We included RCTs comparing the efficacy of BT versus dMT for functional independence among adult patients (≥18) with AIS who meet criteria for IVT. We excluded nonrandomized controlled trials, observational case–control and cohort studies, case reports, review articles and study protocols.

4. Endpoints

The primary endpoint was functional independence at 90 days from stroke onset, defined as a modified Rankin Score of 0–2. Secondary endpoints were (1) successful reperfusion in control tomography at 24–72h (defined by Modified Arterial Occlusive Lesion ≥2), (2) successful reperfusion rate on post-procedural angiography (defined by eTICI 2b-3), (3) mortality at 90 days, (4) and the occurrence of symptomatic intracranial hemorrhage (sICH) within 48 h of stroke onset (defined by Heidelberg criteria).

4.1. Data extraction and risk of bias assessment

Two authors (MCC, GVT) independently extracted relevant data of each included study using standardized extraction formats, concerning study characteristics (eg., author, year of publication, country, number of participants, noninferiority margins), methodological design, baseline characteristics (eg., age, sex, prior medical history, occlusion site, baseline NIHSS and ASPECTS score, door-to-puncture time, needle-to-puncture time) and outcomes including functional independence, successful reperfusion rate, mortality and occurrence of sICH. Missing data was reported, when appropriate. The risk of bias was assessed independently by two authors, using the RoB2 risk of bias assessment tool of the Cochrane Collaboration for Systematic Reviews. Five randomized clinical trials with low risk of bias and one with high risk were found.

4.2. Statistical analysis

Data were analyzed under the intention-to-treat principle. We performed the meta-analysis using Review Manager (RevMan) 5.4 software. The effect measure calculated for primary and secondary endpoints was odds ratio (OR) with a 95 % confidence Interval (CI). Risk difference (RD) and OR with 95 % CI were analyzed to assess non-inferiority for the main outcome of functional independence, within a framework of five non-inferiority margins of −15 %, −10 %, −6.5 %, −5 %, and −1.3 %.[31] Statistical significance was identified with $p \leq 0.05$. Heterogeneity was evaluated with Cochrane's Q test and I^2, with an acceptance of less than 30 % following the guidelines of the Cochrane Manual. Although the I^2 is 0 % in this study, we adopted a more conservative approach pooling data using Mantel-Haenszel random effects. Forest plot graphics were made for the main and secondary outcomes.

5. Results

Six randomized open-label clinical trials were included,[10–15] with 2334 patients enrolled, from which three were conducted in Asian populations. The characteristics of the included studies and baseline characteristics of the population are summarized in Table 1. Five included trials were assessed as low risk of bias, while the DIRECT-MT study was allocated as high risk since protocol violations were reported in which a group of patients did not receive mechanical thrombectomy as treatment (Fig. 1).

The efficacy was analyzed based on functional independence at 90 days and successful reperfusion (Fig. 2). Functional independence was lower in the dMT group compared to BT (48.8 % vs 50.7 %), but there was no significant difference between the two groups (OR = 0.93, 95 % CI 0.79–1.09, p = 0.37; I^2 = 0 %). Successful reperfusion according to tomographic findings at 24–72h was only registered in four studies, reported in 72.8 % of patients in the dMT group, and 74.3 % in the BT group, without significant difference (OR = 0.92, 95 % CI 0.71–1.21, p = 0.56; I^2 = 19 %). Successful reperfusion defined as eTICI score 2b - 3 on the last post-procedural angiogram was significantly lower in the dMT group with 935 of 1161 (80.5 %), compared to 990 of 1169 patients (84.6 %) in BT group (OR = 0.75, 95 % CI 0.60–0.94, p = 0.01; I^2 = 0 %). Mean modified Rankin Score at 90 days did not show a significant difference between the two groups (OR = 0.91, 95 % CI 0.78–1.07, p = 0.45; I^2 = 0 %).

Safety was assessed based on mortality and symptomatic intracranial hemorrhage rate (Fig. 3). No significant difference was found in mortality rates between the two groups (OR = 1.08, 95 % CI 0.86–1.35, p = 0.52; I^2 = 0 %), reported in 15.9 % in the dMT group and 14.9 % in the BT group. The sICH rate was lower in the dMT group with 54 of 1164 (4 %), compared to BT with 64 of 1170 patients (5 %), without significant difference (OR = 0.84, 95 % CI 0.57–1.22, p = 0.36; I^2 = 0 %).

Regarding the non-inferiority analysis, the non-inferiority margins reported by the included studies were 0.8 (OR) for DIRECT-MT and MR CLEAN-NO IV,[10,13] 0.74 (OR) for SKIP,[12] -12 % (RD) on SWIFT DIRECT,[14] and −10 % (RD) for DEVT y DIRECT-SAFE.[11,15] The pooled RD with random effects for functional independence was −2% (95 % CI -6 to 2 %, p = 0.36; I^2 = 0 %) between dMT and BT (Fig. 4).

6. Discussion

This systematic review and meta-analysis showed no significant difference between direct mechanical thrombectomy and bridging therapy in terms of functional independence, mortality, or symptomatic intracranial hemorrhage, suggesting that dMT is non-inferior to BT, based on the analysis of the six main and largest RCTs existing to date. For functional independence at 90 days, defined as a modified Rankin Score of 0–2, the estimates slightly favored BT, but without statistical significance. However, it was shown that patients treated with BT have a higher probability of achieving successful reperfusion defined as classification 2b, 2c or 3 in the eTICI score.

Multiple systematic reviews and meta-analyses had been carried out comparing the efficacy of dMT to BT. *Phan et al*, analyzed 7 cohorts and 5 RCTs, finding no significant differences in terms of functional independence and mortality, but higher reperfusion rates (OR 1.73; 95 % CI 1.04–2.94, I^2 = 13 %) and lower intracranial hemorrhage of any type in the dMT group (OR 0.51; 95 % CI 0.33–0.79, I^2 = 14 %).[20] Similar findings were reported by *Zhang et al*, in which the dMT group had a lower risk of intracranial hemorrhage of any type (OR 0.76, 95 % CI 0.63–0.91, p = 0.00001; I^2 = 29 %).[30] *Wang et al*, included 29 observational studies and one RCT in their review, reporting that the BT group achieved greater functional independence (OR 1.43; 95 % CI, 1.28–1.61, p = 0.014; I^2 = 43 %), as well as lower mortality (OR 0.67; 95 % CI, 0.60–0.75, p = 0.011; I^2 = 23 %) and a higher rate of recanalization (OR 1.23; 95 % CI, 1.07–1.42, p = 0.06; I^2 = 45 %).[29] However, the included studies in Wang meta-analysis are subject to substantial selection bias since patients who did not meet criteria for the administration of IVT were enrolled to the dMT group. Reasons for IVT non-eligibility included prior use of anticoagulants and longer time from stroke onset, which can both influence functional results and bleeding complications.[32] *Kolahchi et al*, when analyzing 4 RCTs and 9 observational studies, found no

Table 1
Characteristics of the randomized clinical trials included in the study.

	DIRECT MT [10]	DEVT [11]	SKIP [12]	MR CLEAN-NO IV [13]	DIRECT-SAFE [15]	SWIFT DIRECT [14]
Author	Yang P.	Zi W.	Suzuki K.	LeCouffe N.	Mitchell P.	Fischer U.
Year of publication	May 2020	January 2021	January 2021	November 2021	July 2022	July 2022
Country	China	China	Japan	Holland, France, Belgium	China, Vietnam, New Zealand, Australia	Swiss
Study design	RCT	RCT	RCT	RCT	RCT	RCT
Number of participants	656	234	204	539	293	408
Period of recruitment	February 2018 to July 2019	May 2019 to May 2020	January 2017 to July 2019	January 2018 to October 2020	June 2018 to June 2021	–
Primary end-point	mRS score at 90 days	Functional independence at 90 days (mRS score 0–2)	Functional independence at 90 days (mRS score 0–2)	mRS score at 90 days	Functional independence at 90 days (mRS score 0–2)	Functional independence at 90 days (mRS score 0–2)
Non-inferiority margin	0.8 (OR)	−10 % (RD)	0.74 (OR)	0.8 (OR)	−0.1 (RD)	−12 % (RD)
Risk of bias (RoB2)	High	Low	Low	Low	Low	Low
Thrombolytic	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.6 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg (120 patients) Tenecteplase 0.4 mg/kg (25 patients)	Alteplase 0.9 mg/kg
Definition of 'sICH'	Heidelberg criteria	Heidelberg criteria	SITS-MOST criteria	Heidelberg criteria	Own definition †	Own definition ‡

	DIRECT MT [10]	DEVT [11]	SKIP [12]	MR CLEAN-NO IV [13]	DIRECT-SAFE [15]	SWIFT DIRECT [14]
N° of participants						
dMT	327	116	101	273	146	201
BT	329	118	103	266	147	207
Mean age						
dMT	69 (61–76)	70 (60–77)	74 (67–80)	72 (62–80)	70 (61–78)	73 (64–81)
BT	69 (61–76)	70 (60–78)	76 (67–80)	69 (61–77)	69 (60–79)	72 (65–81)
Hypertension						
dMT	193 (59.0)	69 (59.5)	61 (60)	121 (44.3)	–	121 (60)
BT	201 (61.1)	74 (62.7)	61 (59)	139 (52.5)	–	118 (57)
Atrial fibrillation						
dMT	152 (46.5)	62 (53.5)	57 (56)	86 (31.5)	–	17(8)
BT	149 (45.3)	62 (53.5)	64 (62)	63 (23.7)	–	22(11)
Diabetes Mellitus						
dMT	59 (18.0)	25 (21.6)	16(16)	40 (14.7)	–	–
BT	65 (19.8)	20 (17.0)	17(17)	50 (18.8)	–	–
ICA, M1, M2 occlusion						
dMT	112 (35.0)	18 (15.5)	41(41)	64 (23.5)	33(23)	57(28)
	161 (50.3)	95 (81.9)	44 (44)	156 (57.4)	80 (55)	133 (66)
	42 (13.1)	3 (2.6)	10(10)	45 (16.5)	21(14)	11(5)
BT	114 (35.0)	17 (14.4)	36(35)	50 (18.8)	31(21)	60(29)
	178 (54.6)	99 (83.9)	35(34)	174 (65.4)	83 (57)	136 (66)
	33 (10.1)	2 (1.7)	2019	40 (15.0)	2316	115
Baseline NIHSS Score						
dMT	17(12–21)	16(12–20)	19(13–23)	16(10–20)	15(11–20)	17(13–20)
BT	17(14–22)	16(13–20)	17(12–22)	16(10–20)	15(10–20)	17(12–20)
Baseline ASPECTS Score						
dMT	9(7–10)	8(7–9)	7(6–9)	9(8–10)	10(9–10)	8(7–9)
BT	9(7–10)	8(7–9)	8(6–9)	9(8–10)	10(9–10)	8(7–9)
Median door-to-puncture time (IQR) (Minutes)						
dMT	84 (67–105)	101 (80–135)	–	63 (50–78)	87 (65–113)	75 (60–90)
BT	85.5 (70–115)	105 (80–132)	–	64 (51–78)	101 (75–127)	80 (63–101)
Median needle-to-puncture time (Minutes)						
BT	26.5*	44*	8*	28(20–41)	37*	24(15–38)

RCT: Randomized clinical trial; mRS: Modified Rankin Score; sICH: symptomatic intracranial hemorrhage; OR: Odds ratio; RD: Risk difference; SITS-MOTS: Safe implementation of thrombolysis in stroke-monitoring Study. †: Large parenchymal hematoma occupying more than 30% of the infarct with substantial mass effect or subarachnoid hemorrhage, combined with deterioration ≥ 4 points in NIHSS score within 36 hours of treatment. ‡: Two definitions of sICH were used. Parenchymal haematoma type 1 or 2, subarachnoid haemorrhage, or intraventricular haemorrhage within 24h (± 6h) associated with an increase ≥4 of NIHSS score. Site-investigator adjudicated evidence of any intracranial haemorrhage and site-investigator adjudicated neurological worsening ≥4 on the NIHSS score, most likely due to radiologically evident intracranial haemorrhage.
dMT: Direct mechanical thrombectomy; BT: Bridging therapy; ICA: Internal carotid artery; M: Middle cerebral artery; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; IQR: Interquartile range. *: Calculated based on the subtraction of the median door-puncture time and the median door-needle time.

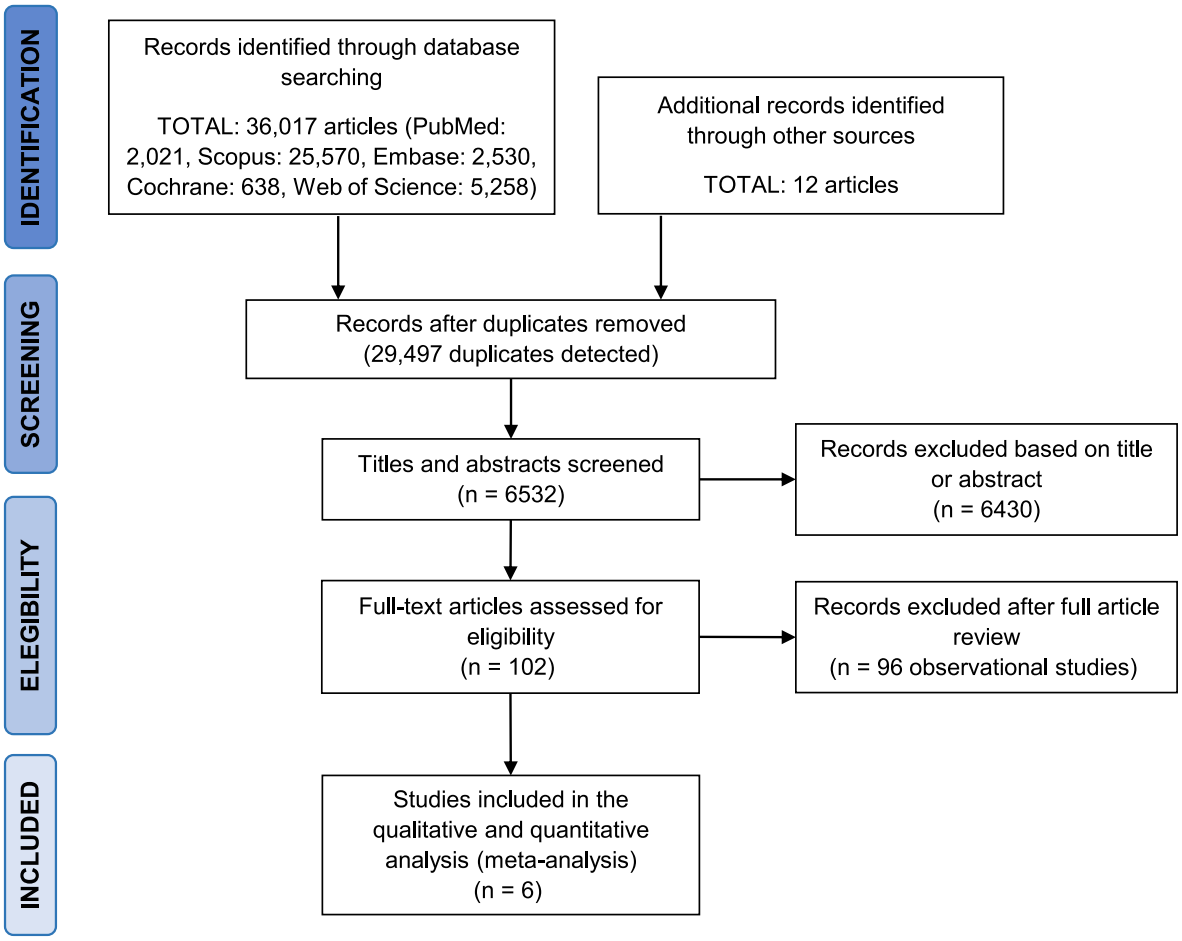

Fig. 1. Prisma flowchart of search strategy and study selection process.

differences regarding functional independence and mortality, but reported higher rates of sICH in the BT group (OR 0.73; 95 % CI, 0.56–0.96, p = 0.02, $I^2 = 0$ %), a result that remained significant only in the observational studies group after subgroup analysis; likewise, successful reperfusion rate was higher for BT in the RCTs subgroup (OR 0.73; 95 % CI, 0.56–0.96, p = 0.02, $I^2 = 0$ %).).[22] The overall results of this study differ from ours in the pooled analysis; however, the RCTs subgroup analysis is consistent with ours. We believe that the main limitation of these publications is that they have a high risk of bias due to the combination of different methodological designs and analysis, which would explain their high heterogeneity;[33] therefore, it is more appropriate to use data provided only from randomized clinical trials to guide clinical practice on the topic.

Lin et al, y *Podlasek, et al*, conducted two meta-analyses including DIRECT MT, DEVT, SKIP, and MR CLEAN-NO IV, using RD and OR as measures of effect size, respectively. Neither authors reported significant differences in terms of functional independence or mortality between the two groups; however, they found that dMT showed lower rates of successful recanalization and intracranial hemorrhage of any type.[31,34] In both studies, no heterogeneity was found between the included RCTs for the main outcome. Their results are consistent with ours, yet it is worth mentioning that our research collected a larger number of clinical trials (DIRECT MT, DEVT, SKIP, MR CLEAN-NO IV, DIRECT-SAFE, and SWIFT DIRECT) and patients, therefore gathering stronger evidence.

The included studies were carried out as non-inferiority trials, designed to demonstrate that the experimental treatment (dMT) is not unacceptably worse than the current standard therapy, with the consensus that the non-inferiority margins (NIM) should be the lower value that would have an important clinical effect.[35] The strictest NIM among the included RCTs was −10 % RD (DEVT and DIRECT-SAFE) or 0.8 OR (DIRECT MT and MR CLEAN-NO IV), whose margins can be considered wide given that the minimum for a relevant clinical difference is up to 5 % according to experts in the area.[36] The pooled RD with random effects for the primary efficacy endpoint of functional independence was −2% (95 % CI -6 to 2 %). The lower bound of −6% fell within the non-inferiority margins of −15 %, −10 %, −6.5 %, but exceeded the stricter limits of −5% and −1.3 %;[37] however, it did fall within the stricter NIM of the included RCTs, which was −10 %. As well, the pooled OR for functional independence was 0.93 (95 % CI 0.79–1.09), with its lower limit of 0.79 falling within the NIM of 0.74 in SKIP. Therefore, dMT is non-inferior to BT, and it may be reasonable to skip IVT and proceed directly with MT in centers equipped for the procedure, even if eligibility criteria for alteplase are met, depending on each case. However, in a context where only few centers have available equipment with trained physicians, the indication for BT continues as the treatment of choice for LVO-AIS, since IVT tends to be the only resource available for reperfusion. Therefore, numerous factors will condition the management provided to the patient; if IVT is available, the patient meets criteria for its use, and transfer of the patient to a higher-level facility will be time-consuming or is not possible, thrombolytic therapy should be given to initiate reperfusion therapy in the shortest time possible. In summary, treatment must be individualized for each patient according to their needs. Nonetheless, considering the wide non-inferiority margins, these findings should be interpreted with caution when recommending dMT over BT.[38]

Our study suggests that BT is associated with higher successful reperfusion rates (OR = 0.77, 95 % CI 0.62–0.96, p = 0.02; $I^2 = 0$ %),

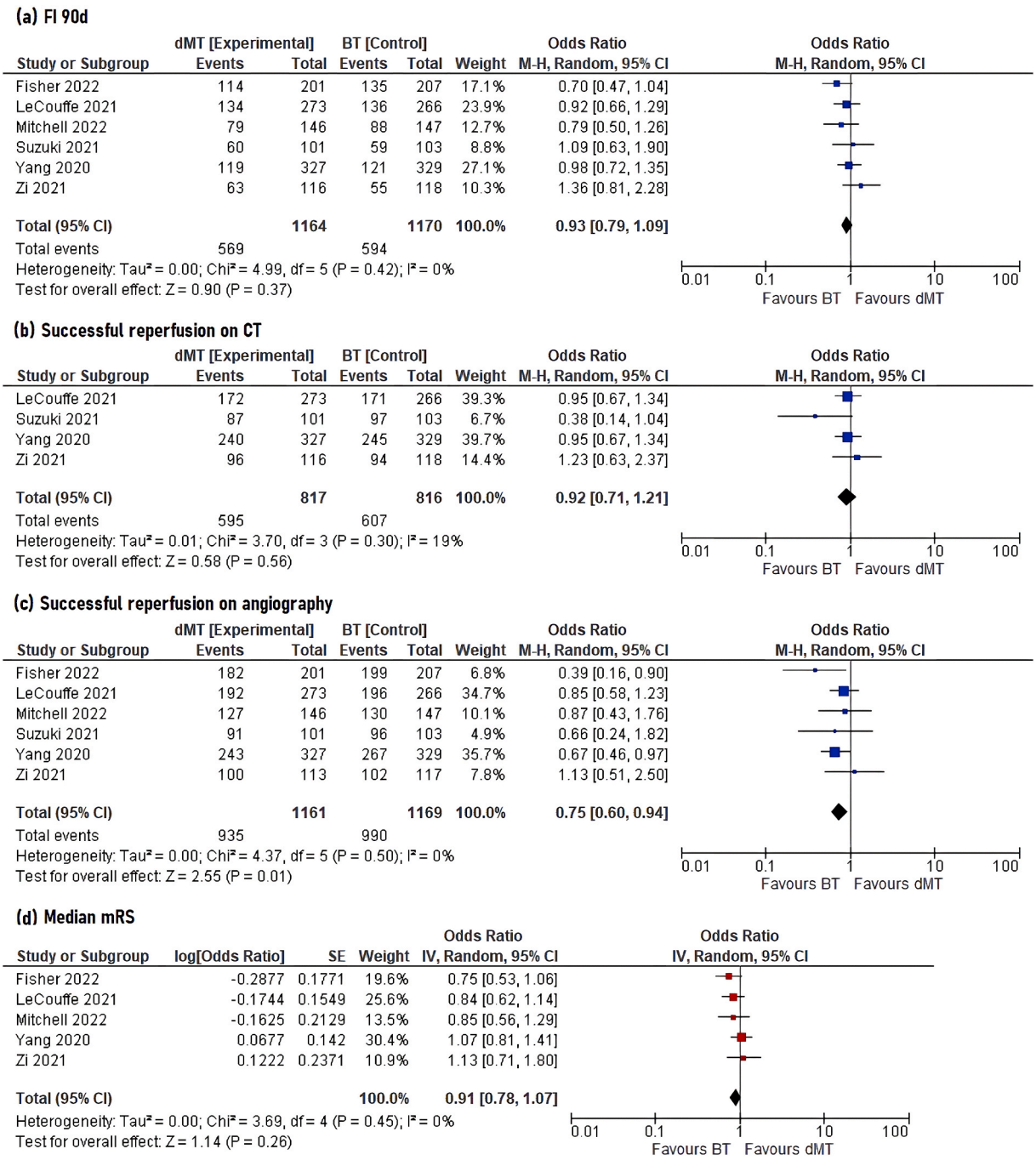

Fig. 2. Forest plots of efficacy compared between direct mechanical thrombectomy and bridging therapy: (a) Functional independence at 90 days (modified Rankin score ≤2); (b) Successful reperfusion in control tomography at 24–72h (Modified Arterial Occlusive Lesion ≥2); (c) Successful reperfusion according to TICI score on post-procedural angiography (eTICI 2b–3); (d) Median 90-day modified Rankin Score. dMT: Direct mechanical thrombectomy; BT: Bridging therapy; FI: Functional independence; CT: Computed tomography; Mrs: Modified Rankin Sctore; OR: Odds ratio; CI: Confidence Interval.

without necessarily implying a significant difference in terms of functional results. SWIFT-DIRECT and SKIP were both studies in which there was a higher rate of successful reperfusion in the BT group according to post-procedural angiography and CT, respectively. However, occlusion of the ICA and the M1 segment predominated among their participants, which theoretically differs from the premise that IVT would be more effective for distal than proximal occlusions.[39] In the BT group, the median time duration from needle-to-groing puncture was 29.7 min, being 8 min the shortest in SKIP trial, and 44 min the largest in DEVT, maintaining the continuous infusion during the endovascular procedure. The non-inferiority findings of dMT compared to BT in terms of functional outcomes could be due to the short time between the two interventions, which would prevent achieving the full therapeutic effect before starting the endovascular treatment. Although there is no record as to why the time between both interventions is short, current guidelines specify that alteplase administration should not delay MT.[8] It was previously suggested that in centers where the "drip and ship" protocol is applied, MT could be delayed;[26,27] however, the difference between the median door-to-groin-puncture time in both groups is nor clinically or statistically significant, being mostly less than 5 min, excepting the DIRECT SAFE trial, in which there is a 14-min delay in the BT group. It is likely that in a different scenario from the trial setting, the time between

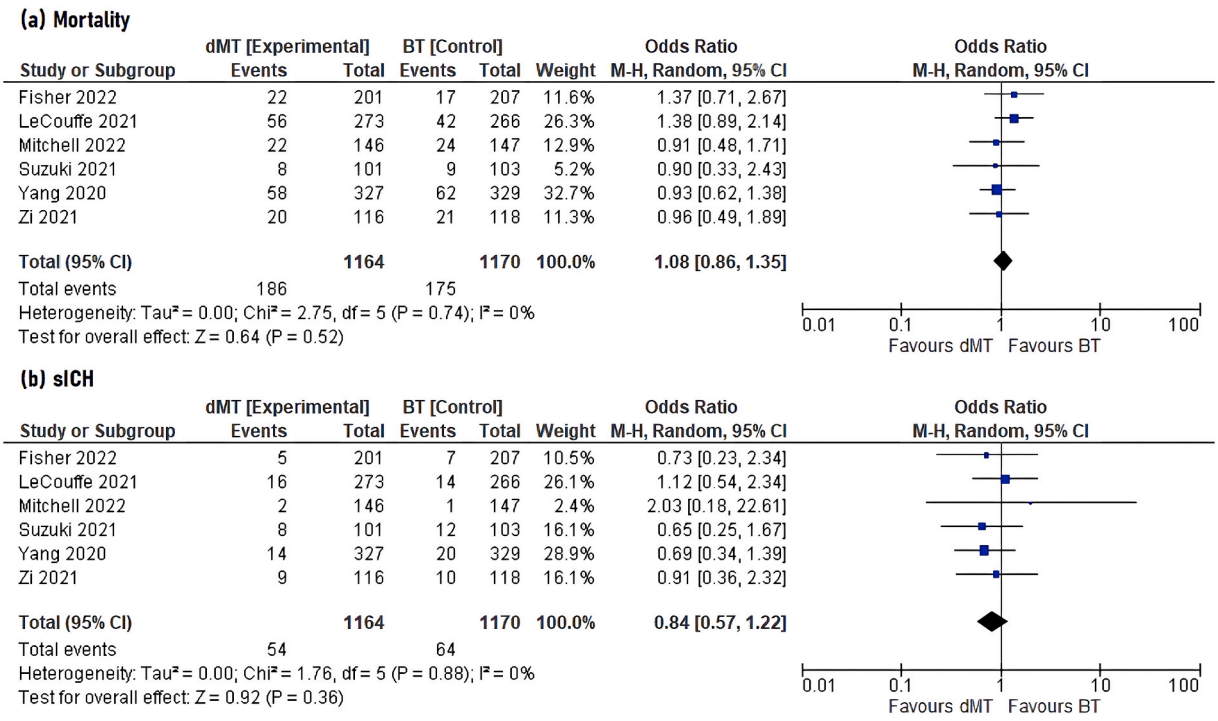

Fig. 3. Forest plots of safety compared between direct mechanical thrombectomy and bridging therapy: (a) 90-day mortality; (b) Symptomatic intracranial hemorrhage. dMT: Direct mechanical thrombectomy; BT: Bridging therapy; sICH: Symptomatic intracranial hemorrhage; OR: Odds ratio; CI: Confidence interval.

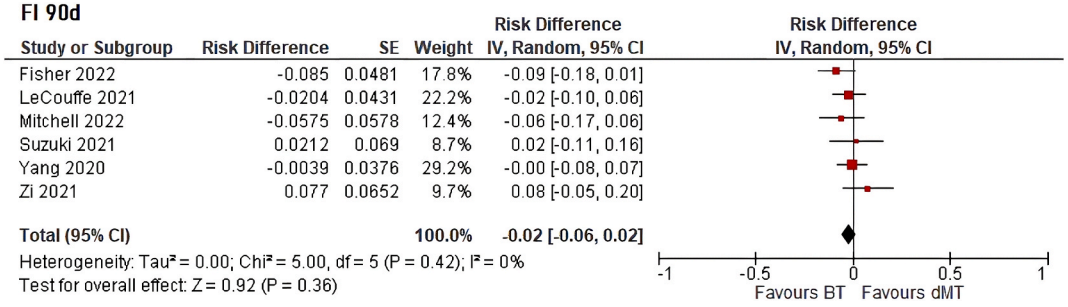

Fig. 4. Forest plot of risk difference of functional independence at 90 days (mRS ≤2) compared between direct mechanical thrombectomy and bridging therapy. dMT: Direct mechanical thrombectomy; BT: Bridging therapy; RD: Risk difference; CI: Confidence Interval.

both interventions would be longer, which may lead to variations in the outcomes. The included studies were conducted in centers equipped to perform both procedures and therefore the results only apply to patients presenting directly to MT-capable centers.

Our analysis has some limitations. First, the "open-label" design of the studies can potentially imply a high risk of bias, and one study was allocated as high risk, which might downgrade the level of evidence. Second, some baseline characteristics such as the NIHSS and ASPECTS score at admission, differed between the two groups, implying different prognoses for each. Third, it was not possible to carry out a subgroup analysis based on patient characteristics such as comorbidities, stroke etiology, and its relationship with the outcomes, since the RCTs do not provide enough information for this purpose. Fourth, the definitions of sICH and successful reperfusion vary across studies. Fifth, most of the studies used alteplase as thrombolytic, except for 25 patients from the DIRECT-SAFE trial in whom tenecteplase was used, limiting our review to the use of alteplase, leaving aside a potentially effective and safe thrombolytic.[40] Finally, the clinical trials included in this study only enrolled patients with AIS in the anterior (carotid) circulation and within a therapeutic window of 4.5 h after onset, so they cannot be extended to populations with posterior circulation strokes or with a delated presentation or unknown time of onset. Likewise, three of the RCTs were conducted in Asian populations, in which there is a significantly higher incidence of intracranial atherosclerotic disease, which limits the generalizability of the findings to non-Asian populations.[41]

7. Conclusions

In conclusion, our systematic review and meta-analysis of RCTs suggest that although BT had a higher rate of successful reperfusion, there is no significant difference in terms of functional independence and mortality at 90 days between dMT and BT in LVO-AIS patients. Direct thrombectomy is non-inferior to bridging therapy based on several non-inferiority margins for the primary endpoint of functional independence. These findings are only applicable to patients presenting directly to an MT-capable center, and populations included in the analyzed studies. Still, the current RCT evidence suggests that in certain scenarios it may be reasonable to skip IVT, and instead proceed with dMT.

Credit author statement

Gustavo Adolfo Vásquez-Tirado: Writing – review & editing, Data curation, Formal analysis. María del Cielo Bravo-Sotero: Writing – review & editing. María del Carmen Isabel Cuadra-Campos: Conceptualization, Data curation, Writing – original draft, Formal analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wnsx.2023.100250.

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ABBREVIATIONS LIST

AIS: Acute ischemic stroke
ASPECTS: Alberta Stroke Program Early CT Score
BT: Bridging therapy
CI: Confidence interval
dMT: Direct mechanical thrombectomy
eTICI: Extended thrombolysis in cerebral infarction score
ICA: Internal carotid artery
ICH: Intracranial hemorrhage
IQR: Interquartile range
IVT: Intravenous thrombolysis
LVO: Large vessel occlusion
mRS: Modified Rankin Score
M1: Middle cerebral artery segment M1
M2: Middle cerebral artery segment M2
MT: Mechanical thrombectomy
NIHSS: National Institutes of Health Stroke Scale
NIM: Non-inferiority margins
OR: Odds ratio
RCT: Randomized clinical trial
RD: Risk difference
sICH: Symptomatic Intracranial hemorrhage
SITS-MOTS: Safe implementation of thrombolysis in stroke-monitoring Study