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Endovascular thrombectomy vs best medical management for late presentation acute ischaemic stroke with large vessel occlusion without CT perfusion or MR imaging selection: A systematic review and meta-analysis

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ABSTRACT

Background: The efficacy and safety of endovascular thrombectomy (EVT) beyond 6 hours from stroke onset for patients with large vessel occlusion (LVO) selected without CT perfusion(CTP) or MR imaging(MRI) is undetermined. We conducted a systematic review and meta-analysis of the current literature comparing outcomes for late presenting patients with LVO treated by best medical management (BMM) with those selected for EVT based only on non-contrast CT(NCCT)/CT angiography(CTA) (without CTP or MRI).

Methods: PRISMA guidelines were employed. The primary outcome was functional independence (modified Rankin Scale 0-2) at 3 months. Secondary outcomes were symptomatic intracranial haemorrhage (sICH) and mortality at 3 months. Data were analysed using the random-effects model.

Results: Six studies of 2083 patients, including three randomised controlled trials, were included; 1271 patients were treated with EVT and 812 patients with BMM. Compared to BMM, patients treated with EVT demonstrated higher odds of achieving functional independence (39.0 % EVT vs 22.0 % BMM; OR = 2.55, 95 %CI 1.61-4.05,p < 0.0001, $I^2 = 74$ %). The rates of sICH (OR = 2.09, 95 %CI 0.86-5.04,p = 0.10) and mortality (OR = 0.62, 95 % CI 0.35-1.10,p = 0.10) were not significantly different between each cohort.

Conclusion: Compared to BMM, late presenting stroke patients selected for EVT eligibility with NCCT/CTA only and treated with EVT achieved significantly higher rates of functional independence at 90 days, without increasing the incidence of sICH or mortality. Whilst these findings indicate that NCCT/CTA only may be used for EVT eligibility selection for patients who present beyond 6 hours from stroke onset, the results should be interpreted with caution due to the substantial heterogeneity between studies.

Abbreviations: EVT, endovascular thrombectomy; BMM, best medical management; AIS, acute ischaemic stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; Alberta Stroke Program Early CT Score, ASPECTS; sICH, symptomatic intracranial haemorrhage; NCCT, non-contrast computed tomography; CTA, computed tomography angiography; LVO, large vessel occlusion.

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Introduction

The DAWN and DEFUSE-3 randomised controlled trials (RCTs) demonstrated the benefit of endovascular thrombectomy (EVT) for large vessel occlusion (LVO) in acute ischaemic stroke (AIS) for patients presenting in the late window (between 6 to 16 or 24 hours from the onset of stroke or last known well) with a significant lesion volume difference (i.e, mismatch) between the perfusion deficit and the ischaemic core selected by advanced neuroimaging (CT perfusion (CTP) or MR imaging (MRI)).[1,2]. However, many institutions have limited access to CT or MR perfusion imaging and instead use non-contrast CT (NCCT) and CT angiography (CTA) to select patients for EVT even for late presenting AIS patients. The recently published MR CLEAN-LATE RCT demonstrated the benefit of EVT treatment for patients presenting between 6 to 24 hours of stroke onset by only using CTA for assessment of collateral flow when determining the EVT imaging eligibility.[3] Furthermore, recent 'large ischaemic core' RCTs demonstrated significantly improved functional outcomes in patients treated with EVT despite less favourable imaging profiles, even up to 24 hours from stroke onset.[4-7]

Various non-randomised studies and meta-analyses have attempted indirect comparisons of functional and safety outcomes of late presenting patients undergoing EVT without CTP or MRI selection compared to those in the early window (within 6 hours of onset), or to those undergoing perfusion-based imaging selection.[8-13] However, a lack of comparison in these studies with a control group of patients managed by best medical management (BMM) hampered assessment of the absolute treatment efficacy and safety outcomes.

Hence, we sought to perform a systematic review and meta-analysis of the current literature. We hypothesised that patients with AIS due to LVO in the anterior circulation who presented beyond 6 hours from stroke onset, and who were selected for EVT based only on NCCT +/- CTA imaging (without CTP or MRI), had improved functional outcomes compared to patients treated solely with BMM.

Methods

Ethics

Informed consent and ethical approval were not required for this systematic review and meta-analysis. No human participant procedure was involved.

Search strategy, study selection, and eligibility criteria

This systematic review and meta-analysis was performed according

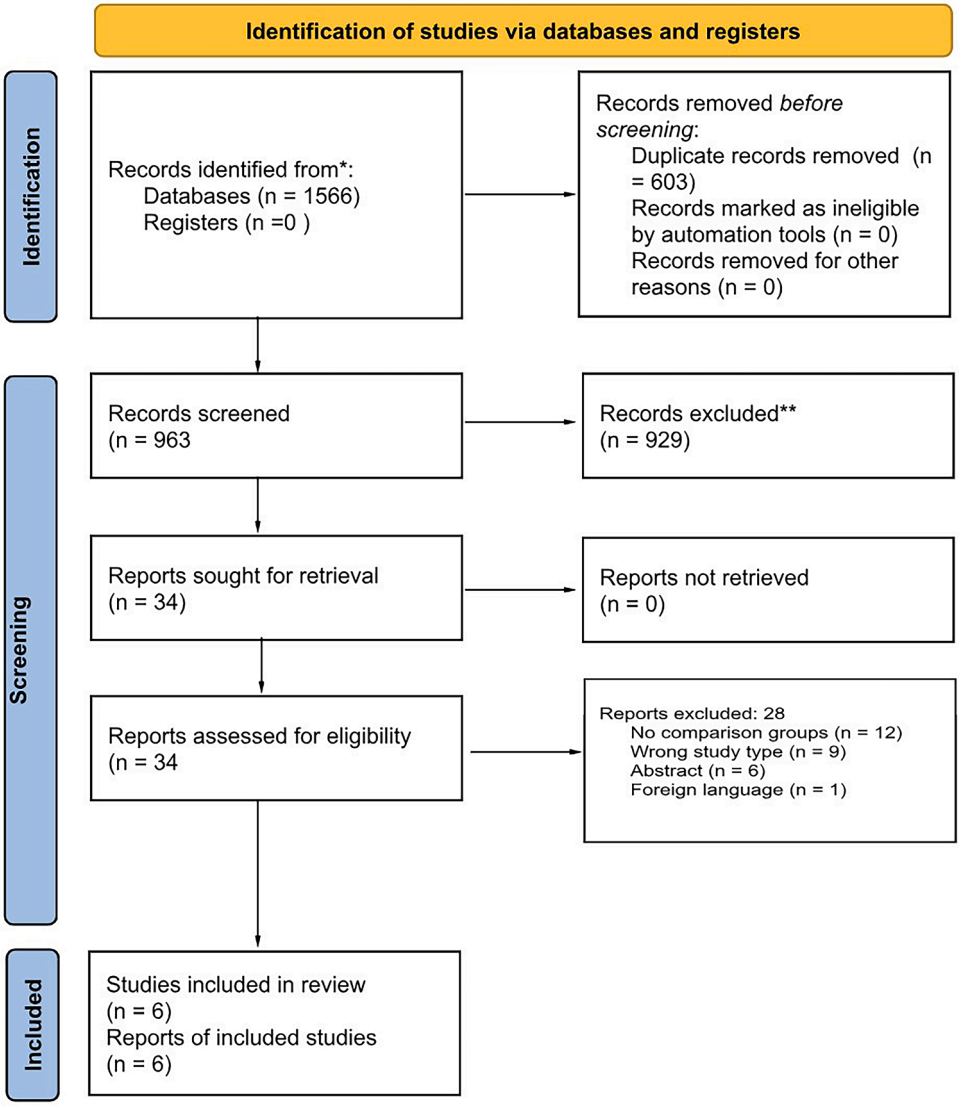

Fig. 1. PRISMA flowchart detailing the inclusion and exclusion criteria. PRISMA indicates preferred reporting items for systematic reviews and meta-analyses.

to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) and the protocol was published before performing the analysis (PROSPERO: CRD42023416922). We systematically searched electronic databases from inception up to May 2024, including PubMed/MEDLINE, EMBASE, and Cochrane. The following keywords were used in combination or individually by using the Boolean operators "OR" and "AND": 'thrombectomy', 'endovascular', 'stroke', 'randomised', 'ICA', 'MCA', 'large vessel occlusion', 'ischaemic stroke', 'endovascular therapy', 'thrombolysis', 'medical management', 'collaterals', 'computed tomography'. The articles were selected in 2 stages. First, the titles and abstracts were screened independently by two reviewers (OM, PD) for relevant studies using Rayyan®. Second, the full texts were assessed independently for eligibility. Any differences were resolved by discussion and consensus. The reference lists of included publications were then hand-searched for additional relevant studies.

Studies were included if they compared one or more clinical and/or procedural outcome of (i) EVT (with or without IV thrombolysis) with (ii) BMM (with or without IV thrombolysis) for adult patients (≥18 years) with AIS due to a LVO in the anterior circulation presenting beyond 6 hours from onset or last known well when EVT eligibility was assessed on only NCCT +/- CTA imaging (without CTP or MRI). Randomised and non-randomised (retrospective and prospective) clinical trials, pre- and post-intervention studies, observational and cohort studies or post-hoc analyses of observational data in trials were included when a control group was reported. Exclusion criteria included animal studies, single-arm studies, abstracts, studies/case series with an overall sample size of fewer than 30 patients, studies that did not have BMM (EVT with/without IVT) in the comparator arm, studies where patients were selected using CTP or MRI, and studies which only included patients with a pre-morbid modified Rankin Scale (mRS) greater than 2. In the event of an overlapping patient population, only the series with the largest number of patients or the most detailed data reported were included.

Data extraction and management

Variables recorded (if available), were study type (retrospective, prospective/RCT), sample size, number of patients in each group (EVT vs BMM), demographics (age, number of males), presence of comorbidities (atrial fibrillation, hypertension, diabetes, coronary artery disease, heart failure, hyperlipidaemia, smoking), clot location (internal carotid artery, middle cerebral artery or tandem occlusion), baseline stroke severity using the National Institutes of Health Stroke Scale (NIHSS), baseline Alberta Stroke Program Early CT score (ASPECTS), prior IV thrombolysis use, witnessed stroke onset, workflow times (onset to randomisation/arterial puncture), successful recanalization defined as modified thrombolysis in cerebral infarction (mTICI 2b-3), functional independence, symptomatic intracranial haemorrhage (sICH), and mortality at 90 days.

Outcome measures

The primary outcome was functional independence (mRS 0-2) at 90 days. The secondary clinical outcomes were mortality at 90 days, and sICH. The definition of sICH was heterogeneous across the studies, though most used the combination of imaging-proven any ICH with an increase in the NIHSS score of 4 or more within 24 hours, or death.

Statistical analysis

Study characteristics and extracted variables were summarised using standard descriptive statistics. Continuous variables were expressed as means and SD, and categorical variables were expressed as frequencies or percentages. Meta-analyses of binary outcomes were expressed as odds ratio (OR) with a 95 % confidence interval (CI). A random-effects model and the Mantel-Haenszel method were used. Tests of heterogeneity were conducted with the Q statistic distributed as a Chi-square variate (assumption of homogeneity of effect sizes). The extent of between-study heterogeneity was assessed with the I^2 statistic. Study heterogeneity I^2 values of >30 % were considered moderate, >50 % considered substantial and >75 % were deemed considerable heterogeneity. A sensitivity analysis of only RCTs was performed to minimise any between-study heterogeneity. Robins-I or Rob-2 tool was used to evaluate the individual risk of bias of each study and was performed by two reviewers (OM, PD), whilst Robvis was used for visualisation.[16] Meta-regression and publication bias were not specifically performed as there were fewer than ten studies included in our meta-analysis.[14] P-values were two-tailed with values <0.05 considered statistically significant. All analyses were implemented using Review Manager 5.4. software.

Data availability statement

All data used for analyses are available within the article and the original publications of included studies.

Results

Included studies and sample characteristics

We screened 963 titles and abstracts, from which 34 full-text articles were evaluated. Of those, 28 studies were excluded based on the reasons shown in the PRISMA flow chart (Fig. 1). A total of 6 studies (3 retrospective and 3 prospective RCTs, including data from the recently presented at ISC 2024 but not yet published RESILIENT-Extend trial),[3,15-19] consisting of 2083 participants, met the inclusion/exclusion criteria for this meta-analysis (Fig. 1). Of these, 1271 patients (61.0 %) were treated with EVT and 812 (39.0 %) with BMM. Table 1 details the baseline characteristics of the included studies.

Outcome measures

Functional independence at 90 days was reported in all studies with a total of 2081 patients, 1271 of which were treated with EVT, and 810 with BMM. Compared to BMM (22.0 %), patients treated with EVT (39.0 %) demonstrated higher odds of achieving functional independence at 90 days (6 studies; OR = 2.55, 95 %CI 1.61-4.05, $p < 0.0001$, $I^2 = 74$ %; Fig. 2). Due to the substantial level of between study heterogeneity ($I^2 = 74$ %), we performed a sensitivity analysis consisting only of the 3 RCTs which showed that, compared to BMM, patients treated with EVT had higher odds of achieving functional independence at 90 days (3 studies; OR = 1.51, 95 %CI 1.05 to 2.16, p = 0.02, $I^2 = 14$ %; Supplementary Figure 1).

There was no significant difference in mortality rate at 90 days between the EVT and BMM groups (5 studies; OR = 0.62, 95 %CI 0.35 to 1.10, p = 0.10, $I^2 = 84$ %; Fig. 3). There was no overall increase in the risk of developing sICH in the EVT group compared to the BMM group (6 studies; OR = 2.09, 95 %CI 0.86 to 5.04, p = 0.10, $I^2 = 67$ %; Fig. 4).

Risk of bias assessment

The evaluation of the risk of bias is summarised in Supplementary Figures 2 and 3. Out of the 6 studies included, 3 were deemed low risk and 3 were deemed moderate risk.

Discussion

Our systematic review and meta-analysis demonstrated that, compared with patients treated by BMM, patients with AIS due to LVO in the anterior circulation presenting between 6 and 24 hours from onset or last known well, who were selected for EVT without CTP or MRI had improved functional outcomes at 90 days, without increased sICH or

Table 1
Details of the included studies.

Study ID	Dhillon et al. 2023		Evans et al. 2018		Nguyen et al. 2024		Nogueira et al. 2024		Olthius et al. 2023		Yang et al. 2023	
Country	United Kingdom		Canada		Europe, North America and Asia		Brazil		Netherlands		China	
Enrolment	2018 to 2022		2013 to 2015		2014 to 2022		2022 to Present		2017 to 2022		2017 to 2018	
Study type	Retrospective		RCT		Retrospective		RCT		RCT		Retrospective	
Comparator	EVT vs BMM		EVT vs BMM		EVT vs BMM		EVT vs BMM		EVT vs BMM		EVT vs BMM	
Total participants, n	150		59		839		245		502		288	
	EVT (n = 74)	BMM (n = 76)	EVT (n = 33)	BMM (n = 26)	EVT (n = 616)	BMM (n = 223)	EVT (n = 126)	BMM (n = 119)	EVT (n = 255)	BMM (n = 247)	EVT (n = 167)	BMM (n = 121)
Age, mean±SD or median (IQR)	68.5 ±14.8	77.1 ±13.9	66.1 (15.2)	67.9 (21.9)	74 (63-83)	77 (66-86)	63 (48-71)	62 (51-72)	74 (64-80)	74 (64-81)	61 (53-73)	67 (54-74)
Men, n (%)	41 (55.4)	34 (44.7)	13 (39.4)	15 (57.7)	276 (44.8)	108 (48.4)	71 (56.3)	62 (52.1)	107 (42.0)	134 (54.3)	94 (56.3)	60 (49.6)
NIHSS, median (IQR)	18 (12-22)	19 (16-25)	14 (4)	17 (12)	16 (11-20)	15 (10-20)	16 (14-19)	16 (12-19)	10 (6-17)	10 (6-18)	12 (10-15)	13 (10-16)
ASPECTS, median (IQR)	7 (6-8)	7 (6.75-8)	9 (2)	8.5 (3)	8 (7-9)	8 (7-9)	8 (6-8)	7 (6-8)	9 (7-10)	8 (7-9)	9 (8-10)	8 (8-9)
IVT, n (%)	6 (8.1)	12 (15.8)	8 (24.2)	15 (57.7)	120 (19.5)	37 (16.6)	31 (24.6)	25 (21.0)	12 (4.7)	19 (7.7)	43 (25.7)	15 (12.4)
Witnessed Stroke Onset, n (%)	28 (37.8)	32 (42.1)	NR	NR	62 (10.1)	29 (13.0)	NR	NR	35 (13.7)	21 (8.5)	114 (68.3)	70 (57.9)
Successful Recanalisation (mTICI 2b-3)	71 (95.9)	-	28/32 (87.5)	-	537 (87.2)	-	92/111 (82.9)	-	154/190 (81.1)	-	143 (85.6)	-
Stroke Location, n (%)												
ICA	20 (27.0)	20 (26.3)	9/31 (29.0)	7 (26.9)	180 (29.2)	38 (17.0)	34 (27.0)	33 (27.7)	37 (14.5)	39 (15.8)	43 (25.7)	23 (19.0)
MCA	54 (73.0)	56 (73.7)	22/31 (71.0)	19 (73.1)	436 (70.8)	185 (83.0)	106	98	215 (84.3)	202 (81.8)	107 (64.1)	69 (57.0)
Tandem Occlusion	NR	NR	NR	NR	NR	NR	NR	NR	51/248 (21.0)	57/236 (24.0)	17 (10.2)	29 (24.0)
CVS Risk Factors, n (%)												
Hypertension	35 (47.3)	42 (55.3)	22 (66.7)	21 (80.8)	461 (74.8)	154 (69.1)	NR	NR	142/254 (55.9)	118/245 (48.2)	83 (49.7)	63 (52.1)
Diabetes	18 (24.3)	11 (14.5)	5 (15.2)	7 (26.9)	168 (27.3)	39 (17.5)	NR	NR	35/254 (13.8)	39/246 (15.9)	30 (18.0)	26 (21.5)
Atrial Fibrillation	14 (18.9)	19 (25.0)	14 (42.4)	11 (42.3)	239	81	NR	NR	51/254 (20.1)	53/246 (21.5)	52 (31.1)	28 (23.1)
Previous stroke/TIA	9 (12.2)	13 (17.1)	NR	NR	NR	NR	NR	NR	51/254 (20.1)	40/246 (16.3)	23 (13.8)	16 (13.2)
Workflow time (minutes)												
Onset to randomisation/puncture (mean±SD or median, IQR)	966.4 ±523.4	NR	468 (179)	405 (107)	660 (480-858)	708 (540-894)	750 ±258	756 ±252	665 (485-862)	630 (478-851)	NR	NR

ASPECTS = Alberta Stroke Program Early CT Score, BMM = Best Medical Management, ICA = internal carotid artery, IQR = interquartile range, IVT = intravenous thrombolysis, EVT = endovascular thrombectomy, NIHSS = National Institutes of Health Stroke Scale, mTICI = modified thrombolysis in cerebral infarction, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, TIA = transient ischaemic attack

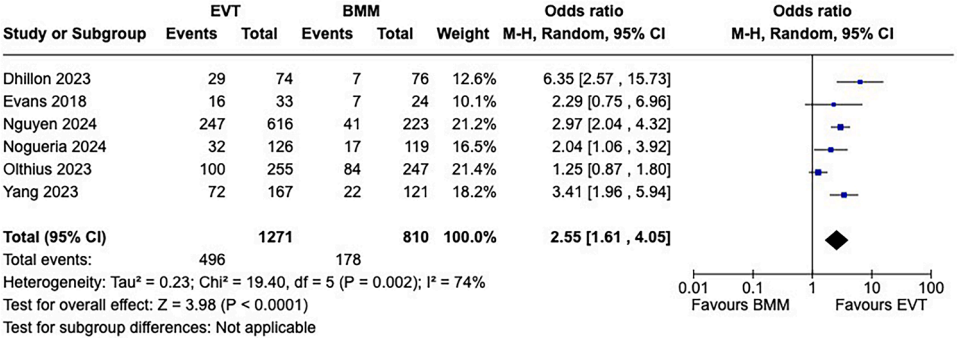

Fig. 2. Forest plot demonstrating the odds ratio of functional independence at 90 days of endovascular thrombectomy (EVT) and best medical management (BMM).

mortality rates.

Overall, our findings indicate that NCCT +/- CTA (without CTP or MRI) could be used to select patients who present between 6 to 24 hours from stroke onset for EVT, with net treatment benefit and comparable safety outcomes. Although advanced imaging (CTP or MRI) in the late window may reliably select 'slow progressors' with a higher chance of achieving improved functional outcomes following EVT compared to 'fast progressors',[20,21] our findings suggest that a proportion of patients with a limited ischaemic core and adequate collateral supply may also be feasibly selected with NCCT +/- CTA alone.

The AURORA pooled analysis of individual patient data of RCTs failed to demonstrate a statistically significant treatment benefit of EVT

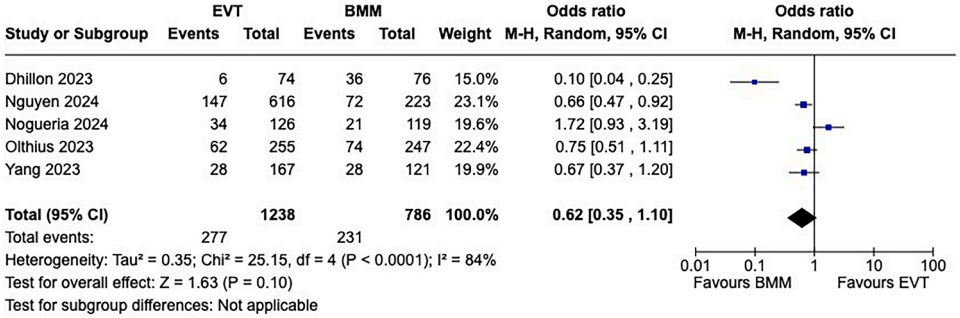

Fig. 3. Forest plot demonstrating the odds ratio of mortality rates at 90 days of endovascular thrombectomy (EVT) and best medical management (BMM).

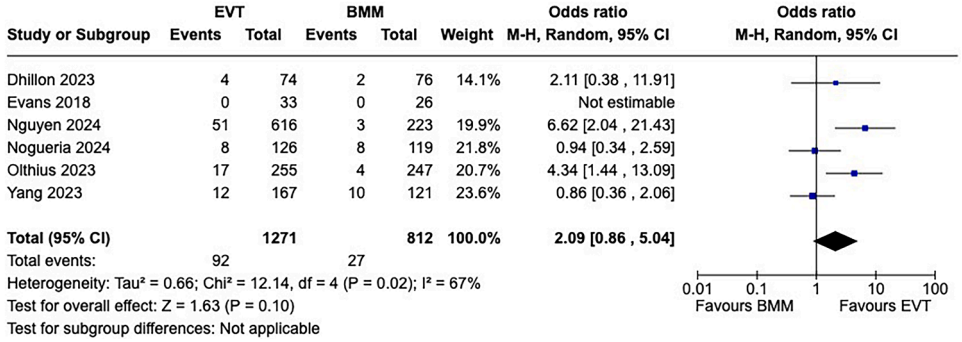

Fig. 4. Forest plot demonstrating the odds ratio of symptomatic intracranial haemorrhage (sICH) rates of endovascular thrombectomy (EVT) and best medical management (BMM).

in patients selected without CTP or MR imaging in the late window, likely due to the modest sample size (n = 132).[22,23]. However, despite excluding DAWN or DEFUSE-3 eligible patients, the MR CLEAN-LATE trial demonstrated improved functional outcome amongst EVT-treated patients compared to the BMM cohort.[3] The RESILIENT-Extend trial completed in Brazil, involving a publically funded healthcare system with limited resources, also demonstrated a net treatment benefit of EVT 8 to 24 hours from stroke onset, although a similar effect was not identified for those above 68 years of age.[18] Although the large positive treatment effect size seen in the DAWN and DEFUSE-3 trials was not replicated in the MR CLEAN Late and RESILIENT-Extend trials, the increased number of patients that might benefit from EVT treatment despite having a less favourable imaging profile would widen the potential treatment impact on the population as a whole.

Previous studies and meta-analyses attempting to indirectly compare advanced imaging (CTP or MRI) with non-advanced imaging (NCCT +/- CTA only) selection protocols in late presenting patients have mostly demonstrated no difference in the functional outcomes following EVT.[9,10,12,13] Direct comparisons of the superiority of advanced versus non-advanced imaging protocols are difficult and subject to a denominator bias given the varying clinical inclusion criteria across studies.[24] Furthermore, the lack of a control group of BMM patients in the previous meta-analyses has hampered the assessment of the absolute treatment efficacy for patients selected without CTP or MRI in the late window.

The American Heart Association/American Stroke Association (AHA/ASA) and the European Society of Minimally Invasive Neurological Therapy (ESMINT) guidelines recommend the CTP or MRI-based imaging criteria utilised in the DAWN and DEFUSE-3 trials to select patients eligible for EVT when presenting in the late time window.[25,26] However, due to limited access to urgent CTP or MRI, many institutions in various parts of the world routinely utilise more widely available NCCT +/- CTA imaging only to estimate the infarct size and collateral circulation even in the late window. In addition, there is a time penalty associated with advanced imaging acquisition, an increased radiation exposure from acquisition of CTP and recent evidence that patients with large ischaemic cores at presentation benefit from EVT, with or without perfusion imaging.[5,7]

The main strength of this meta-analysis is in allowing assessment of the treatment efficacy by including RCTs and a comparator arm of patients who underwent BMM only following imaging selection without CTP or MRI in the late window. There are also several limitations. First, results from this study need cautious interpretation due to the non-randomised and observational nature of three of the studies included, potentially leading to selection bias. There was substantial between study heterogeneity which may have been due to the differences in study design and/or baseline characteristics of the population investigated. However, we performed a sensitivity analysis of RCTs only to mitigate this effect, the results of which again demonstrated the improvement in functional independence in favour of EVT. Second, despite imaging selection for EVT using only NCCT +/- CTA in the late window, heterogeneous clinical and imaging thresholds for eligibility were utilised across the studies. Third, the paucity of data on the outcomes according to the clot location, ASPECTS or infarct size, collateral circulation scores and time from stroke onset precluded sub-group analysis. Fourth, one of the included studies, the RESILIENT-Extent trial, was presented but not yet published at the time of the meta-analysis, and hence, although unlikely, the results of the published data analysis could vary. Last, to fully understand the impact of treatment on clinical outcomes an ordinal shift mRS analysis should also be performed on pooled individual patient data.

Conclusion

Our meta-analysis demonstrated that compared to BMM, late presenting AIS patients with LVO assessed for EVT eligibility using only NCCT +/- CTA and treated with EVT achieved significantly higher rates of functional independence at 90 days without increasing the incidence of sICH or mortality. Whilst these findings indicate that NCCT +/- CTA

(without CTP or MRI) may be used for EVT eligibility selection for AIS patients with LVO who present beyond 6 hours from stroke onset or last known well, the results should be interpreted with caution due to the substantial heterogeneity between studies.

CRediT authorship contribution statement

Permesh Singh Dhillon: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Omar Marei:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Anna Podlasek:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Waleed Butt:** Writing – review & editing, Methodology, Investigation. **Hal Rice:** Writing – review & editing. **Laetitia de Villiers:** Writing – review & editing. **Vinicius Carraro do Nascimento:** Writing – review & editing. **Norman McConachie:** Writing – review & editing. **Robert Lenthall:** Writing – review & editing. **Sujit Nair:** Writing – review & editing. **Luqman Malik:** Writing – review & editing. **Pervinder Bhogal:** Writing – review & editing. **Robert A Dineen:** Writing – review & editing, Supervision. **Timothy J England:** Writing – review & editing, Supervision.

Declaration of competing interest

No disclosures or competing interests declared by the authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.108002.

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