RESEARCH ARTICLE

IV Thrombolysis Initiated Before Transfer for Endovascular Stroke Thrombectomy

A Systematic Review and Meta-analysis

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Abstract

Background and Objectives

The role of IV thrombolysis (IVT) in patients with large vessel occlusions (LVOs) administered before transfer from a primary stroke center (PSC) to a comprehensive stroke center (CSC) is questioned.

Methods

We included observational studies of patients with an LVO receiving IVT at a PSC before their endovascular thrombectomy (EVT) transfer compared with those receiving EVT alone. Efficacy outcomes included excellent or good functional outcomes (modified Rankin Scale [mRS] scores of 0–1 or 0–2, respectively) and reduced disability (mRS shift analysis) at 3 months. Safety outcomes included symptomatic intracranial hemorrhage (sICH) within 48 hours and 3-month all-cause mortality. Associations are reported with crude odds ratios (ORs) and adjusted ORs (aORs).

Results

We identified 6 studies, including 1,723 participants (mean age: 71 years, 51% women; 53% treated with IVT at a PSC). The mean onset-to-groin puncture time did not differ between the 2 groups (mean difference: −20 minutes, 95% CI −115.89 to 76.04). Patients receiving IVT before transfer had higher odds of 3-month reduced disability (common OR = 1.98, 95% CI 1.17–3.35), excellent (OR = 1.70, 95% CI 1.28–2.26), and good (OR = 1.62.95% CI 1.15–2.29) functional outcomes, with no increased sICH (OR = 0.87, 95% CI 0.54–1.39) or mortality (OR = 0.55, 95% CI 0.37–0.83) risks. In the adjusted analyses, patients receiving IVT at a PSC had higher odds of excellent functional outcome (aOR = 1.32, 95% CI 1.00–1.74) and a lower probability for mortality (aOR = 0.50, 95% CI 0.27–0.93).

Discussion

Patients with LVO receiving IVT at a PSC before an EVT transfer have a higher likelihood of excellent functional recovery and lower odds of mortality, with no increase in sICH and onset-to-groin puncture times, compared with those transferred for EVT without previously receiving IVT.

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Glossary

aOR = adjusted OR; **CSC** = comprehensive stroke center; **EVT** = endovascular thrombectomy; **LVO** = large vessel occlusion; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PSC** = primary stroke center; **RCT** = randomized controlled clinical trial; **ROBINS-I** = Risk of Bias in nonrandomized Studies; **sICH** = symptomatic intracranial hemorrhage.

Recent randomized controlled clinical trials (RCTs) have evaluated the noninferiority of direct endovascular thrombectomy (EVT), bypassing IV thrombolysis, in patients with an acute large vessel occlusion (LVO) otherwise eligible for IV thrombolysis.[1-4] The population of these RCTs consisted of patients presenting directly to comprehensive stroke centers (CSCs) capable of providing EVT, and thus, they cannot provide any insight on the utility of IV thrombolysis administration in patients with acute LVO presenting initially to a primary stroke center (PSC) capable of providing IV thrombolysis but requiring subsequent transfer to a CSC for EVT (drip and ship).[5,6]

As stroke reperfusion therapies are rapidly evolving in the era of EVT, the utility of prompt IV thrombolysis administration in the management of patients with a suspected acute LVO has been questioned by some.[7] In the present systematic review and meta-analysis, we evaluate the utility of IV thrombolysis administered in PSCs for patients with confirmed LVO before their transfer to a CSC for EVT.

Methods

The present systematic review and meta-analysis is reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses statement[8] and adheres to the Meta-analyses Of Observational Studies in Epidemiology proposal.[9] The protocol of the systematic review and meta-analysis has been submitted in PROSPERO (submission ID: 333020).

Two authors (A.H.K. and G.T.) performed independent searches in MEDLINE and Scopus databases to identify published cohort studies (prospective or retrospective) or RCTs reporting outcomes of patients with an acute LVO, who received IV thrombolysis within a PSC before their transfer to a CSC for EVT and compared with patients with an acute LVO transferred to receive EVT alone at a CSC without previously receiving IV thrombolysis at the PSC. The complete search algorithm used in MEDLINE is available in eAppendix 1 (links.lww.com/WNL/C581). The last literature search was performed on May 1, 2022. No language or other restrictions were applied in the literature search algorithm. Studies reporting IV thrombolysis administration within a CSC were excluded. Case reports, case series, and conference abstracts were excluded from further consideration.

Each study was evaluated for risk of bias and methodological quality using the Risk of Bias in nonrandomized Studies (ROBINS-I) tool.[10] The ROBINS-I tool assesses the quality of a study in the domains of methodology to address confounding, selection of participants, classification of intervention, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result. Risk of bias was assessed in each study separately by 2 investigators (A.H.K. and L.P.). Any discrepancies between the 2 evaluators were resolved with consensus after consultation with a third investigator (G.T.). Results of the risk of bias assessments were displayed both graphically and in narrative form.

The primary outcome of interest was the probability for good functional outcome at 3 months, defined as modified Rankin Scale (mRS) scores 0–2,[11] between patients with an acute LVO presenting at a PSC receiving IV thrombolysis before transfer for EVT and those only receiving EVT at a CSC following transfer from a PSC with no previous IV thrombolysis administration. We also assessed the probabilities for 3-month excellent functional outcome, defined as mRS scores of 0–1, and reduced disability between the 2 groups, defined as ≥1-point reduction across all mRS scores at 3 months in shift analysis.[11] Safety outcomes of interest included symptomatic intracranial hemorrhage (sICH), according to the definition used in each study, and all-cause mortality at 3 months. In case of data unavailability in the original publication for any of the aforementioned outcomes of interest for patients transferred from a PSC to a CSC for EVT, we requested the aggregate data after contacting the corresponding authors of the relevant eligible studies.

For each outcome of interest, we extracted or calculated the crude odds ratios (ORs) or common ORs in the case of functional improvement across the distribution of the 3-month mRS scores, with the corresponding 95 CIs. For authors responding positively to our request for aggregate data we additionally asked, they provide us with the ORs and corresponding 95% CIs for the associations of interest adjusted for identical potential confounders such as age, baseline NIH Stroke Scale (NIHSS) score, and onset-to-groin puncture time. For the continuous outcomes of age and onset-to-groin puncture time reported in median values and corresponding interquartile ranges, we estimated the sample mean and SD using the quantile estimation method[12] before calculating the pooled estimates. The authors who provided previously unpublished aggregate data were also included as coauthors in the current meta-analysis (A.S., M.T.F., J.P., N.G., R.W.R., and N.H.M.-K.).

All crude and adjusted estimates were pooled under the random-effects model (DerSimonian and Laird). Heterogeneity between studies was assessed with the Cochran Q and

Table 1 Characteristics of Included Studies

First author (year)	Location	Study design	Recruitment period	No. patients		Women (%)		Mean age (SD), y		Mean NIHSS score (SD)		Mean OTGP time (SD/IQR)	
				BT	EVT alone	BT	EVT alone	BT	EVT alone	BT	EVT alone	BT	EVT alone
Chang et al. (2020)[14]	Single center, United States	Prospective cohort	January 2016 to June 2019	39	17	21 (54)	11 (65)	69.2 (19.3)	68.5 (16.5)	16.3 (6.3)	17.6 (7.4)	255.4 (58.7)	431.8 (322.5)
Froehler et al. (2017)[15,a]	Multicenter, United States	Retrospective analysis of prospective registry	August 2014 to June 2016	229	216	200 (45)		66.9 (14.6)		18.0 (5.5)		276.5 (77.3)	283.4 (93.7)
Goyal et al. (2019)[16,a]	Single center, United States	Retrospective analysis of prospective database	2013 to 2017	103	71	55 (63)	32 (37)	63.9 (15.4)	63.1 (14.1)	15.0 (6.4)	17.6 (8.5)	308 (258–371)	448 (323–616)
Purrucker et al. (2021)[17,a]	Single center, Germany	Retrospective analysis of prospective registry	2017 to 2020	394	320	217 (55)	181 (57)	74.5 (11.8)	76.0 (12.0)	15.9 (7.9)	14.7 (8.2)	285 (233–356)	400 (261–626)
Regenhardt et al. (2021)[18,a]	Multicenter, United States	Retrospective analysis of prospective registry	2018 to 2020	98	160	48 (49)	81 (51)	70.2 (17.9)	71.0 (14.8)	12.3 (9.6)	12.7 (8.9)	547 (318–846)	240 (204–294)
Sarraj et al. (2021)[19,a]	Multicenter, United States	Prospective cohort	January 2016 to February 2018	55	21	—	—	—	—	—	—	201 (148–263)	196.5 (127–267)

Abbreviations: BT = bridging therapy (administration of IV thrombolysis at a primary stroke center before transfer to a comprehensive stroke center for endovascular treatment); EVT = endovascular thrombectomy alone (no prior administration of IV thrombolysis); IQR = interquartile range; NIHSS = NIH Stroke Scale; OTGP = onset-to-groin puncture.
[a] Providing unpublished data.

I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, whereas values of at least 75% indicated considerable heterogeneity.[13] Small-study effect, as a surrogate indicator for publication bias, was assessed graphically in the funnel plots of the unadjusted and adjusted probabilities of excellent functional outcome between the 2 groups. All analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Standard Protocol Approvals, Registrations, and Patient Consents

The current work is a systematic review and aggregate data meta-analysis of already published studies, and therefore, no patient consent or ethics approval was required.

Data Availability

Data sets used for this meta-analysis will be made available by request.

Results

A literature search in MEDLINE and Scopus retrieved 559 and 557 records, respectively. After excluding duplicates, we identified 6 eligible studies (eFigure 1, links.lww.com/WNL/C581), including 1723 participants (53% treated with IV thrombolysis at a PSC). Characteristics of the studies that were eligible for the meta-analysis are presented in Table 1.[14-19] The mean age of included patients was 71 years, while 51% were women. The mean onset-to-groin puncture time did not differ between the pooled groups of patients receiving IV thrombolysis and those treated with EVT alone (mean difference: −19.93 minutes, 95% CI −115.89 to 76.04; eFigure 2).

All 6 observational studies were judged to have at least a moderate risk of bias, whereas 3 of them[14,17,18] were considered to have a serious risk of bias (eFigure 3, links.lww.com/WNL/C581). Included studies were generally rated poorly during our assessment for bias due to confounding (significant baseline differences were evident between the 2 groups) and measurement of outcomes (outcome assessment was not blinded). A moderate risk of bias was disclosed in the domain of missing data (eFigure 4) because outcome assessment was not available for a small proportion of patients in 3 studies.[14,15,18]

In the unadjusted analyses (Table 2), patients receiving IV thrombolysis at a PSC before EVT transfer had higher odds of 3-month excellent outcome (crude OR = 1.70, 95% CI 1.28–2.26; I^2 = 14%; Figure 1A), a higher likelihood of 3-month good outcome (crude OR = 1.62, 95% CI 1.15–2.29; I^2 = 47%; Figure 2A), a higher probability of 3-month reduced disability (common OR = 1.98; 95% CI 1.17–3.35; I^2 = 56%; eFigure 5, links.lww.com/WNL/C581), and a lower probability for all-cause 3-month mortality (crude OR = 0.55, 95%

Table 2 Overview of the Unadjusted and Adjusted Analyses

	Unadjusted analyses			Adjusted analyses		
Outcome	**N studies**	**Effect estimate (95% CI)**	**I^2, *p* for Cochran Q**	**N studies**	**Effect estimate (95% CI)**	**I^2, *p* for Cochran Q**
Excellent functional outcome	5	OR = 1.70 (1.28–2.26)	14%, 0.33	5	aOR = 1.32 (1.00–1.74)	0%, 0.66
Good functional outcome	5	OR = 1.62 (1.15–2.29)	47%, 0.11	5	aOR = 1.22 (0.95–1.58)	0%, 0.73
Functional improvement	3	cOR = 1.98 (1.17–3.35)	56%, 0.10	2	acOR = 1.58 (0.89–2.83)	0%, 0.63
Mortality	6	OR = 0.55 (0.37–0.83)	46%, 0.10	5	aOR = 0.50 (0.27–0.93)	69%, 0.01
Symptomatic ICH	6	OR = 0.87 (0.54–1.39)	0%, 0.62	5	aOR = 0.72 (0.42–1.25)	0%, 0.47

Abbreviations: acOR = adjusted common OR; aOR = adjusted OR; cOR = common OR; ICH = intracranial hemorrhage; OR = odds ratio.

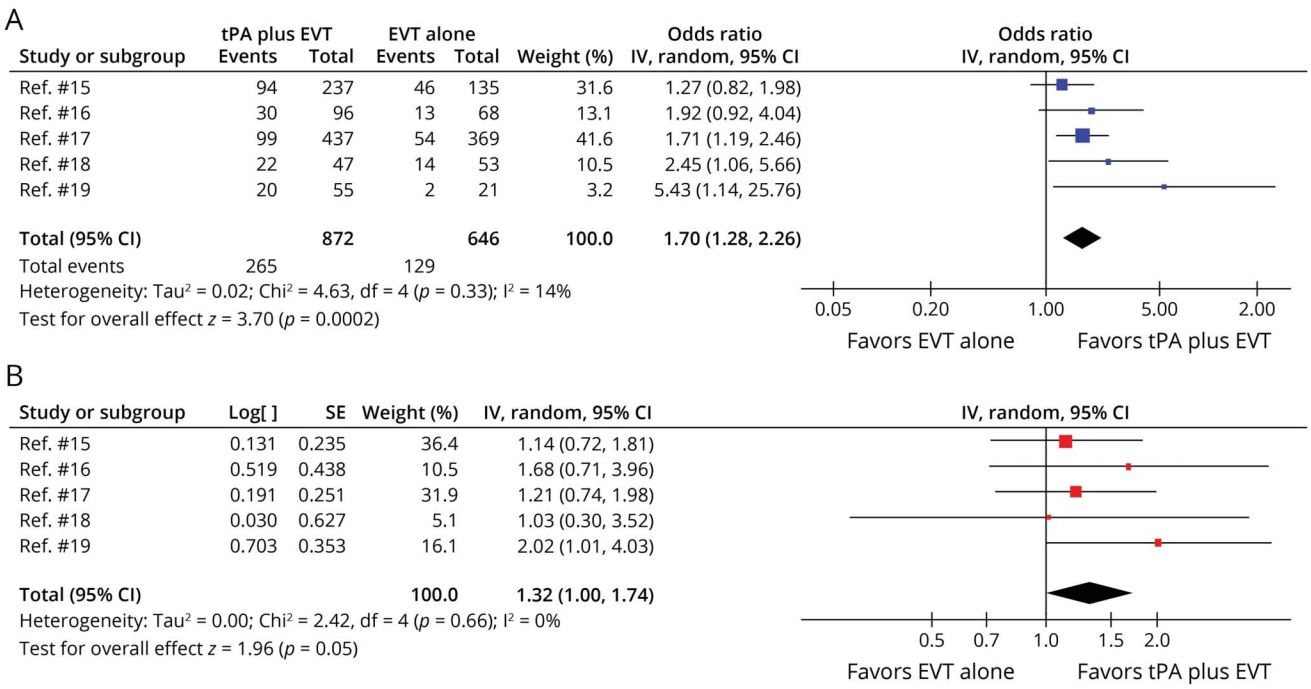
CI 0.37–0.83; I^2 = 46%; Figure 3A), compared with patients receiving EVT alone at a CSC. There was no increase in the odds of sICH (crude OR = 0.87, 95% CI 0.54–1.39; I^2 = 0%; eFigure 6).

In the analyses adjusted for identical potential confounders (Table 2), drip and ship patients receiving IV thrombolysis at a PSC had higher odds of excellent functional outcome (adjusted OR [aOR] = 1.32, 95% CI 1.00–1.74; I^2 = 0%; Figure 1B) and a lower probability for all-cause mortality at 3 months (aOR = 0.50, 95% CI 0.27–0.93; I^2 = 69%; Figure 3B), compared with patients receiving EVT alone at a CSC, with no IV thrombolysis pretreatment. No differences were found between the 2 groups in the probability of 3-month reduced disability (adjusted common OR = 1.58, 95% CI 0.89–2.83; I^2 = 0%; eFigure 5, links.lww.com/WNL/C581), good functional outcome (aOR = 1.22, 95% CI 0.95–1.58; I^2 = 0%; Figure 2B), or the odds of sICH (aOR = 0.72, 95% CI 0.42–1.25; eFigure 6). Funnel plot inspection revealed the presence of asymmetry in the unadjusted, but not adjusted probability for 3-month excellent functional outcome (eFigure 7, links.lww.com/WNL/C581).

Discussion

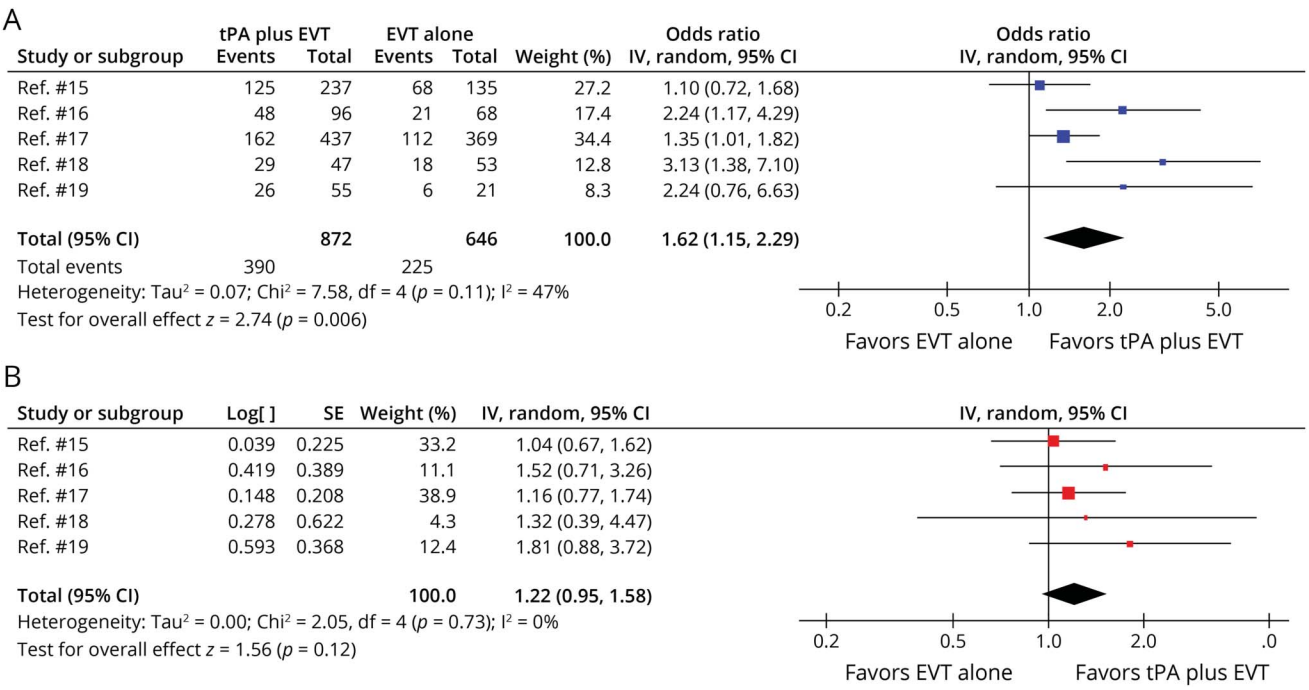
Our meta-analysis showed that patients with an acute LVO presenting at a PSC receiving IV thrombolysis before their transfer to a CSC for EVT have a higher likelihood of excellent

Figure 1 Probability for Excellent Functional Outcome at 3 Months



(A) Unadjusted and (B) adjusted probability of excellent functional outcome (modified Rankin Scale score 1 or less) at 3 months between patients receiving IV thrombolysis before transfer for endovascular thrombectomy compared with patients receiving endovascular thrombectomy alone.

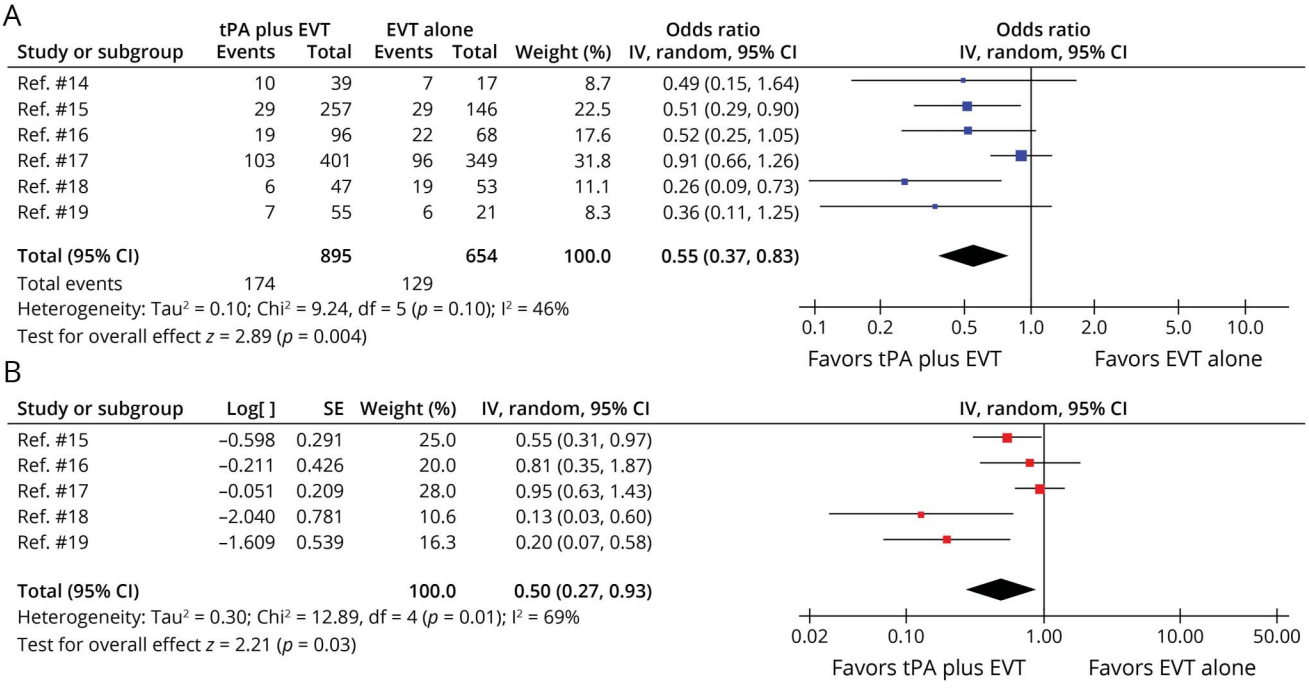
Figure 2 Probability for Good Functional Outcome at 3 Months



(A) Unadjusted and (B) adjusted probability of good functional outcome (modified Rankin Scale score 2 or less) at 3 months between patients receiving IV thrombolysis before transfer for endovascular thrombectomy compared with patients receiving endovascular thrombectomy alone.

functional recovery (albeit with a CI including 1.00) and lower odds of all-cause mortality, with no increase in the rate of sICH, and no delay in onset-to-groin puncture time when compared with those receiving only EVT. Our findings line up with the recent guidelines from the European Stroke Organisation and the European Society for Minimally Invasive

Figure 3 Probability for All-Cause Mortality at 3 Months



(A) Unadjusted and (B) adjusted probability of all-cause mortality at 3 months between patients receiving IV thrombolysis before transfer for endovascular thrombectomy compared with patients receiving endovascular thrombectomy alone.

Neurological Therapy including a recommendation for eligible stroke patients with anterior circulation LVO admitted to a center without EVT capability to receive IV thrombolysis before their rapid transfer to an EVT-capable center.[20]

IV thrombolysis administration at the PSC has been highlighted as an independent predictor of partial or complete recanalization on arrival at the CSC.[21] Early recanalization en route from the PSC to the CSC has been associated with better functional outcomes and seems to occur more frequently in the setting of more distal occlusions and smaller clot burden at baseline imaging.[22] Alteplase-induced successful recanalization can amend the need for EVT in approximately 1 of 10 patients with acute LVO presenting directly to a CSC.[23] This percentage has been reported to be twice as high (1 in 5) for those receiving IV thrombolysis at a PSC and being subsequently transferred for EVT to a CSC.[24,25] In addition, IV thrombolysis with tenecteplase appears to be even more effective than alteplase in averting EVT and can be associated with greater improvement of clinical outcomes in LVO patients treated with bridging therapy.[26,27] Finally, IV thrombolysis–mediated recanalization has a significant effect on the cost-effectiveness of interhospital transfers for EVT and is particularly relevant for elderly patients with moderate or severe stroke syndromes.[28]

Patients with an acute LVO presenting initially to a PSC seem to have higher odds of receiving IV thrombolysis before EVT compared with those presenting directly to a CSC.[14] In the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) registry, 42% of EVT cases initially presented to a PSC, with a median time from stroke onset to arrival at the PSC of 53 minutes and 83% of them receiving IV thrombolysis.[29] Based on data from the same registry, the respective median time between PSC arrival and dispatch (door-in – door-out) was 85 minutes, whereas the median transfer time from the PSC to the CSC was 28 minutes.[30] Onset-to-treatment time is known to correlate not only with the elapsed time between IV thrombolysis bolus and recanalization but also with the probability of 3-month favorable functional outcomes.[31] Patients with acute ischemic stroke receiving IV thrombolysis within 60 minutes from symptoms onset, also referred as the golden hour, have substantially higher odds of early neurologic recovery, successful recanalization, and favorable 3-month functional outcomes.[32]

Despite the strengths of our systematic review and meta-analysis, including unpublished data from 5 of 6 included studies, some limitations need to be acknowledged. First, it should be highlighted that included studies are observational cohort studies, and thus, there is a high probability of baseline imbalances and unmeasured confounders between groups. The main limitation of all studies included in the meta-analysis was the lack of information concerning the reasons for no administration of IV thrombolysis and no record of the patients who were recanalized before arrival to the CSC. Likewise, the proportion of patients who were not transferred to a CSC for EVT due to early recanalization associated with IV thrombolysis administration at the PSC is unknown. As highlighted in our bias assessment (eFigures 3 and 4, links.lww.com/WNL/C581), there are also concerns on the validity of reported outcomes given the lack of blinded outcome assessment and missing data. In funnel plots, inspection asymmetry was uncovered in the unadjusted but not adjusted estimates (eFigure 7). Although there is a possibility for the presence of publication bias, the discrepancy between unadjusted and adjusted estimates in funnel plot assessment could be perceived as a further indication of the presence of true differences on the effect of IV thrombolysis in studies with imbalances in baseline patient characteristics between the 2 groups of interest.[33] Second, the aim of this work was to assess the utility of IV thrombolysis administered in eligible patients before transfer for EVT and not to address the question of whether there is a greater benefit in receiving IV thrombolysis early at a PSC before being transferred to a CSC for EVT (drip and ship approach) compared with the direct transfer to a CSC, bypassing the PSC (mothership approach).[34] Finally, it should be noted that IV alteplase was used as the thrombolytic agent in included studies. Based on evidence from RCTs performed in hospital settings, patients with acute ischemic stroke with an LVO receiving IV tenecteplase had significantly better recanalization and clinical outcomes compared with those receiving IV alteplase.[26] On the same line, IV tenecteplase was also found to be superior to IV alteplase for early reperfusion when given in the setting of a mobile stroke unit.[35]

In conclusion, the current meta-analysis provides supporting evidence for the prompt administration of IV thrombolysis in eligible patients with an acute LVO presenting to a PSC before their transfer to a CSC for EVT. Efforts in PSCs should concentrate in reducing the door-in to door-out times, which represent the single biggest modifiable factor in onset to recanalization times. Importantly, we did not find evidence that administration of IV thrombolysis delayed door-in to door-out as onset-to-groin times were similar between the 2 groups.

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