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Systematic review

Simplified stroke imaging selection modality for endovascular thrombectomy in the extended time window: systematic review and meta-analysis

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ABSTRACT

Background The impact of imaging selection modality on clinical outcomes of endovascular thrombectomy (EVT) in the 6–24-hour time window remains undetermined. We compared the clinical outcomes of a simplified stroke imaging selection modality using non-contrast computed tomography (NCCT)±CT angiography (CTA) with using advanced CT perfusion (CTP).

Methods PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials were searched from inception to 1 May 2022 to compare NCCT±CTA and CTP for patient selection for EVT in late-presenting stroke with large vessel occlusions (LVO). The primary outcome was the proportion of patients achieving functional independence (modified Rankin Scale score 0–2) within 180 days. The secondary outcomes included mortality within 90 days, successful recanalization, and any intracranial hemorrhage.

Results A total of 3419 patients in six articles were included in this meta-analysis. There was no significant difference between NCCT±CTA (no-CTP) and CTP in functional independence either in overall or subgroup analysis. However, the mortality in the no-CTP group was higher than in the CTP group. Furthermore, within the DAWN/DEFUSE 3-like subgroup, there were no significant differences in mortality, successful recanalization, and any intracranial hemorrhage between the two groups.

Conclusion There was no significant difference between the simplified NCCT±CTA modality and the advanced CTP modality. The use of NCCT±CTA may represent a reasonable option for selecting patients for EVT in the extended time window, especially in the absence of CTP and acute phase MRI capabilities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The simplified non-contrast CT (NCCT)±CT angiography (CTA) imaging selection modality has been researched in some studies which showed that it may be safe and beneficial for endovascular thrombectomy (EVT) in selected patients in the extended time window. The effect and safety of NCCT±CTA compared with CTP is controversial and needs to be further elucidated.

WHAT THIS STUDY ADDS

⇒ The simplified NCCT±CTA imaging selection modality achieved comparable functional independence to CTP imaging in overall and subgroup analysis.

⇒ There were no significant differences in mortality, successful recanalization, and any intracranial hemorrhage between the two imaging selection modalities in certain populations (DAWN/DEFUSE 3-like).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that the simplified imaging selection modality (NCCT±CTA) may be used as an alternative to advanced CTP imaging in selecting patients with late-presenting large vessel occlusion for EVT.

⇒ The analysis could provide an optional imaging strategy to EVT for patients in the extended time window in centers that lack advanced imaging capabilities.

⇒ Further well-conducted prospective randomized controlled trials should be performed to evaluate the necessity of CTP for patient selection in EVT.

Endovascular thrombectomy (EVT) has become the standard of care for patients with acute ischemic stroke caused by large vessel occlusion (AIS-LVO) within 6 hours after symptom onset.[1 2] Over the past 4 years the landmark DAWN (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trials have further demonstrated a robust benefit of EVT within the 6–24-hour window,[3 4] opening the indications for EVT in the extended time window. Given that these two trials required the use of CT perfusion (CTP) or MRI in all patients, the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization/European Society for Minimally Invasive Neurological Therapy (ESO/ESMINT) guidelines recommend advanced imaging for selecting patients with LVO stroke in the extended time window.[2 5 6]

However, the strict application of advanced imaging may exclude some patients from treatment due to the lack of availability of urgent CTP or

MRI in many stroke centers globally.[7] Recommendations are not even suggested for centers without advanced imaging. Several simplified, less restrictive imaging selection modalities involving more specific imaging parameters such as the Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast computed tomography (NCCT)[8] or the collateral circulation status on CT angiography (CTA) have been researched in some studies, and showed that the NCCT±CTA imaging selection modality may be safe and beneficial for EVT in selected patients in the late time window.[9–12]

This study aims to compare the more simplified NCCT±CTA imaging with CTP imaging for patient selection for EVT in the extended window. A meta-analysis of published high-quality observational studies was conducted.

METHODS

Search strategy and selection criteria

A review protocol was published for this study in PROSPERO (CRD 42022322356). The PICOS (Patient population, Intervention, comparator, Outcome, Study design) framework was used to search for relevant articles: (1) the patient population was adult patients undergoing EVT with AIS-LVO within 6 and 24 hours after symptom onset or after the time that patients were last seen well (LSW); (2) the intervention was the more simplified NCCT±CTA imaging selection modality for EVT; (3) the comparator was CTP imaging for patient selection; (4) the outcomes were functional independence, mortality, successful recanalization, and any intracranial hemorrhage; and (5) the study design was all study types except case reports. This meta-analysis was conducted in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[13]

We searched PubMed, Embase, Web of Science and Cochrane Central Register of Controlled Trials from inception to 1 May 2022 for all studies that compared NCCT±CTA versus CTP imaging selection in late presentation of stroke with LVO. We created search strategies using a combination of the following keywords (stroke, thrombectomy, and imaging selection) and the relevant controlled vocabulary. Details of the literature search strategies and full search terms are shown in online supplemental table S1. We checked the reference lists of original studies, review articles, other meta-analyses, editorials, and conference abstracts to look for other potentially eligible studies. We imported all references generated from searches into the reference manager EndNote X9 (Thompson Reuters, Philadelphia, Pennsylvania, USA). Eeach article was screened initially using the title and the abstract, and subsequently by reading the full text to select eligible articles based on the selection criteria. Two review authors (ZD and SD) independently assessed each study. Disagreements between the two reviewers were resolved by a senior coauthor (JZ).

The Newcastle–Ottawa Scale (NOS) was used to score the quality of the observational studies and the study quality was classified as good, fair, or poor based on the Agency of Healthcare Research and Quality (AHRQ) standards.

Data extraction

Outcome measures used in each study were extracted independently by two reviewers (ZD and SD), which included the rates of achieving functional independence (mRS score 0–2) within 180 days, mortality within 90 days, successful reperfusion (defined as grade 2b or 3 (>50% of the affected territory) on the modified Treatment in Cerebral Infarction (mTICI) scale), and any intracranial hemorrhage.

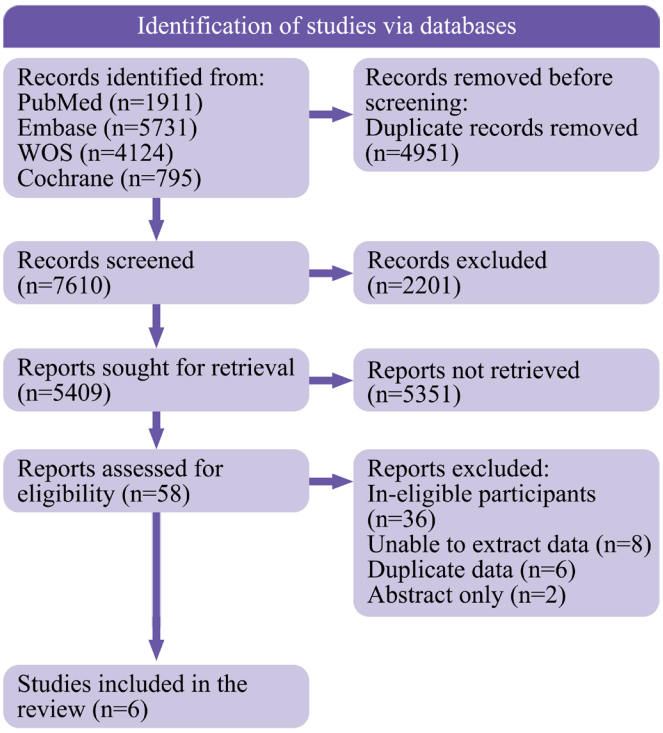

Figure 1 Results of the systematic review of the literature for this study. The database searches returned 12 561 studies. Of these, six were ultimately included in the analysis. The reasons for exclusion are shown.

Meta-analyses

Analyses were performed using Review Manager (RevMan Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Microsoft Excel Version 2019 (Microsoft Corp). The meta-analysis summary calculated the relative risk (RR) with 95% CIs of the NCCT±CTA imaging selection modality (no-CTP) versus the CTP imaging selection modality for the above outcomes. Statistical significance was defined as $p \leq 0.05$. Statistical heterogeneity among studies was evaluated using the Cochrane Q test and the I^2 statistic. P values <0.1 and I^2 statistic >50% represented substantial heterogeneity between studies. If I^2 >50% for the pooled analysis, we sought to explore possible sources of heterogeneity.

RESULTS

Study characteristics

The results of the literature search are shown in figure 1. Initially 12 561 records were searched, then 58 potentially eligible full-text reports were retrieved after removing duplicate records (n=4951) and excluding the records through the systematic screening of titles and abstracts (n=7552). Ultimately, six articles with 3419 patients were included in the meta-analysis.

The characteristics including study, year of publication, data source, study design, the number of countries, sample size, site of occlusion, premorbid mRS score, age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score and ASPECTS before treatment in the six studies are shown in table 1. All six studies were evaluated with high quality of the scores ranging from 7 to 9 by the NOS (see online supplemental table S2).

Table 1 Characteristics of included studies

Study/ year of publication	Data source	Study design	No of countries	Total no of patients	Site of occlusion	Collateral assessment	Premorbid mRS score	No of patients no-CTP/CTP		Median age (years)	Male (%)	Baseline NIHSS (median)	Baseline ASPECTS (median)
Dekker, 2021[14]	MR CLEAN Registry	Post hoc analysis	1	106	ICA\M1\ M2\M3\ A1\A2	Yes	0–2	85	21	No-CTP: 67.4 CTP: 65.8	No-CTP: 43.5 CTP: 47.6	No-CTP: 16 CTP: 13	No-CTP: 9 CTP: 7
Almekhlafi, 2022[9]	SOLSTICE Consortium	Pooled multicenter analysis	11	608	ICA\M1\ M2	Yes	NA	229	379	No-CTP: 70 CTP: 70	No-CTP: 46.7 CTP: 51.2	No-CTP: 15 CTP: 16	No-CTP: 8 CTP: 8
Herzberg, 2021[15]	German Stroke Registry	Post hoc analysis	1	208	ICA\M1\ M2	No	0–2	79	129	No-CTP: 75.8 CTP: 72.3	No-CTP: 49.4 CTP: 67.4	No-CTP: 16 CTP: 16	No-CTP: 8 CTP: 8
Dhillon, 2022[16]	National Stroke Registry of UK	Post hoc analysis	1	1046	NA	No	0–1	668	378	NA	No-CTP: 51.6 CTP: 55.6	No-CTP: 16 CTP: 16	NA
Nogueira, 2021[7]	Trevo Retriever Registry	Retrospective study	12	247	ICA\M1\ M2	No	0–2	67	180	No-CTP: 65.8 CTP: 66.7	No-CTP: 58.2 CTP: 41.1	No-CTP: 16 CTP: 15	No-CTP: 8 CTP: 8
Nguyen, 2021[17]	CLEAR study	Retrospective study	5	1204	ICA\M1\ M2	No	0–2	534	752	No-CTP: 71 CTP: 69	No-CTP: 48.9 CTP: 46	No-CTP: 17 CTP: 16	No-CTP: 8 CTP: 8

mRS, modified Rankin Scale; no-CTP, no CT perfusion; CTP, CT perfusion; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; M3, M3 segment of middle cerebral artery; A1, A1 segment of the anterior cerebral artery; A2, A2 segment of the anterior cerebral artery; NA, not available.

Clinical outcomes

When comparing the simplified NCCT±CTA imaging selection modality (no-CTP group) with the CTP imaging selection modality (CTP group), there was no significant difference in the rate of achieving functional independence (mRS scores of 0–2) between the two groups (RR 0.97; 95% CI 0.83 to 1.13; p=0.68). However, the mortality in the no-CTP group was higher than in the CTP group (RR 1.21; 95% CI 1.04 to 1.40; p=0.01) (figure 2 and figure 3). No heterogeneity was detected in functional independence (p=0.56, I^2=0%) and mortality (p=0.68, I^2=0%).

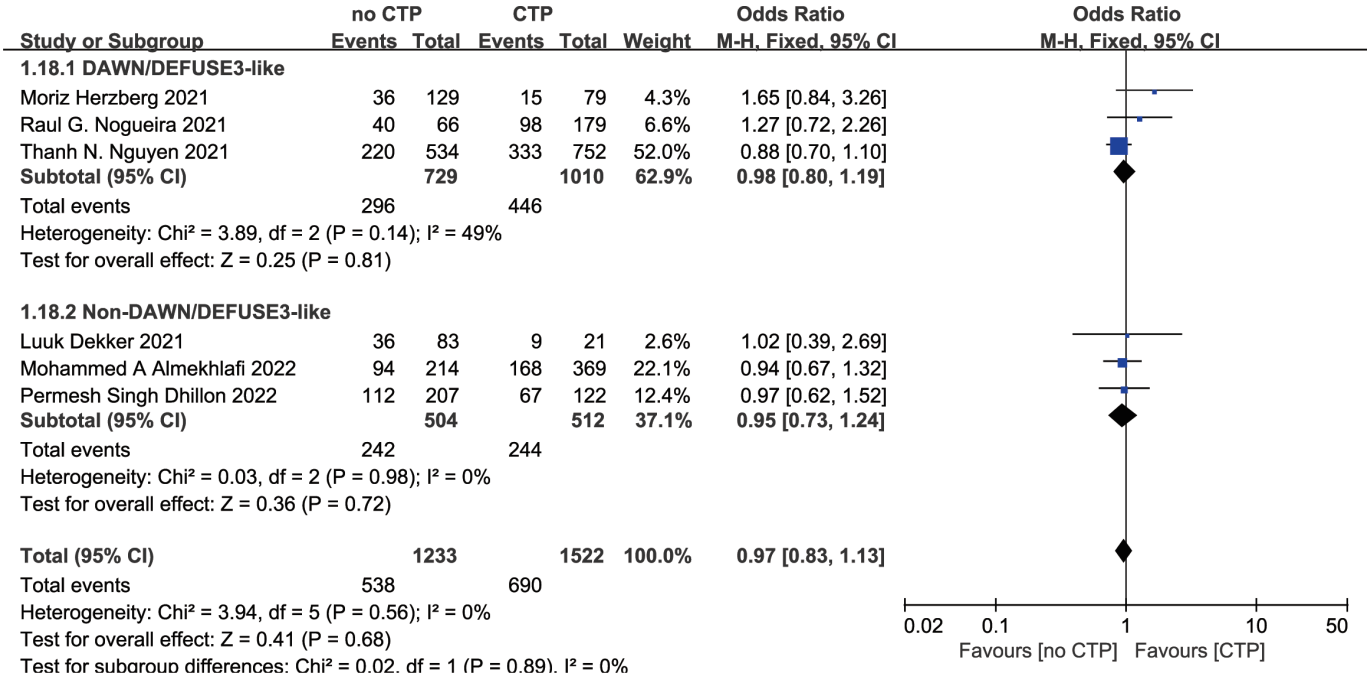

Figure 2 Forest plot of achieving functional independence (modified Rankin Scale score 0–2) within 180 days in patients with large vessel occlusion comparing the NCCT±CTA imaging selection modality (no-CTP group) versus the CTP imaging selection modality (CTP group). NCCT, non-contrast CT; CTA, CT angiography; CTP, CT perfusion.

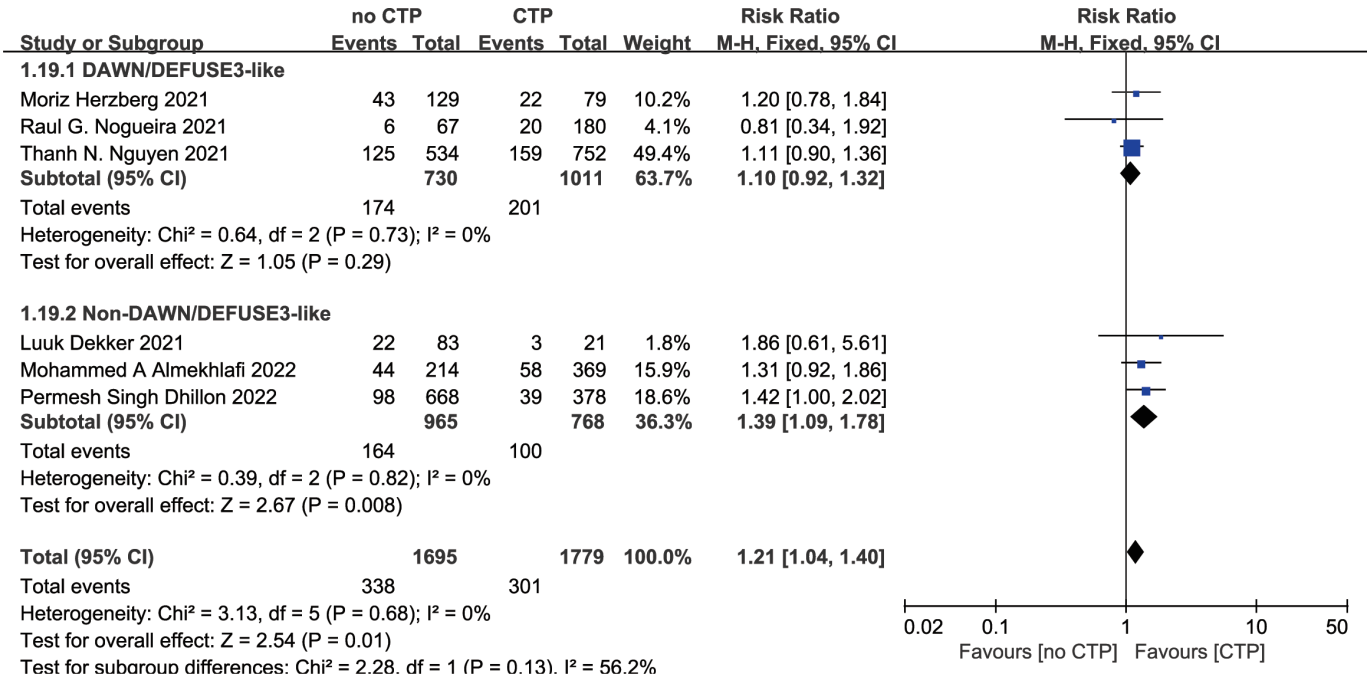

Figure 3 Forest plot of mortality within 90 days in patients with large vessel occlusion comparing the NCCT±CTA imaging selection modality (no-CTP group) versus the CTP imaging selection modality (CTP group). NCCT, non-contrast CT; CTA, CT angiography; CTP, CT perfusion.

Regarding the other clinical outcomes, there was substantial heterogeneity in the rates of successful recanalization and any intracranial hemorrhage among the included studies (p=0.002, I^2=73% and p=0.02, I^2=64%, respectively; figure 4). Subgroup analyses were performed to explore possible sources of heterogeneity. Based on the vital baseline characteristics of the DAWN and DEFUSE 3 trials, the studies were divided into a DAWN/DEFUSE 3-like subgroup (baseline National Institutes of Health Stroke Scale (NIHSS) ≥6, internal carotid artery or M1 or M2 occlusion, and premorbid mRS score 0–2) and a non-DAWN/DEFUSE 3-like subgroup. In the DAWN/DEFUSE 3-like subgroup the heterogeneity among the studies dramatically decreased with successful recanalization (p=0.28, I^2=22%) and any intracranial hemorrhage (p=0.35, I^2=4%). In contrast, the heterogeneity of studies in the non-DAWN/DEFUSE 3-like subgroup significantly increased to 87% and 83%. In the DAWN/DEFUSE 3-like subgroup there were no significant differences in the rates of mortality, successful recanalization, and any intracranial hemorrhage between the no-CTP group and the CTP group (figure 3 and figure 4).

Moreover, no significant differences were found in functional independence in the overall or subgroup analysis (figure 2).

DISCUSSION

DAWN and DEFUSE 3 were two landmark stroke trials that changed the care paradigm for patients with LVO stroke who presented within 6–24 hours of symptom onset. The two trials rely entirely on advanced imaging (such as CT/MR perfusion or diffusion-weighted imaging) to select patients because of its high specificity in identifying patients who will benefit from treatment. Unfortunately, due to potential treatment delays,[14] extra radiation exposure, contrast load, costs, and resource usage, it is an enormous challenge to implement the extended window protocols in many centers worldwide. It does not imply that perfusion or diffusion imaging is the only method for selecting patients. The use of perfusion imaging for EVT patient selection has become increasingly controversial.

The clinical core mismatch was used to guide patient selection in the DAWN trial,[3] and the DEFUSE 3 trial relied on perfusion imaging mismatch to choose eligible patients.[4] According to previous studies, fewer than 25% of all stroke patients meet the DAWN and DEFUSE 3 imaging criteria.[15] Another study showed that a significant proportion of patients who did not meet the DAWN and DEFUSE 3 imaging criteria achieved functional independence 3 months after EVT.[16 17] A recent study showed that routine CTP screening reduced the chance of undergoing EVT by 40% compared with a cohort identified through NCCT±CTA, whereas no difference in clinical outcomes was observed.[14] It indicates that extension window selection criteria may be too strict. With more inclusive selection paradigms, a larger proportion of late presenting patients could be treated.

The effect and safety of imaging selection paradigms in patients with AIS-LVO are still debated in the literature. Some studies have suggested no significant differences in the rates of 90-day functional independence, 90-day mortality, successful reperfusion and symptomatic intracranial hemorrhage.[7 18] Other studies have shown that the patients selected by CTP more often had symptomatic intracranial hemorrhage, but all the other outcomes were comparable.[19 20] However, the result of the recent study was inconsistent with previous research. Compared with non-perfusion neuroimaging, acquisition of CTP for EVT was related to improved functional outcomes in the late time windows.[21]

In this meta-analysis, when comparing the more simplified NCCT±CTA imaging selection modality (no-CTP) with the CTP imaging selection modality, the rate of functional independence was similar whether the strict DAWN/DEFUSE 3-like criteria or more inclusive overall criteria were applied. The NCCT±CTA imaging selection modality led to equivalent outcomes to those in patients selected by CTP. Two factors could explain the equivalence of outcomes across the imaging modalities. First, it has recently been reported that several studies have demonstrated the correlation between NCCT-ASPECTS and CTP core volumes.[22 23] Second, in the extended time window the sensitivity of NCCT

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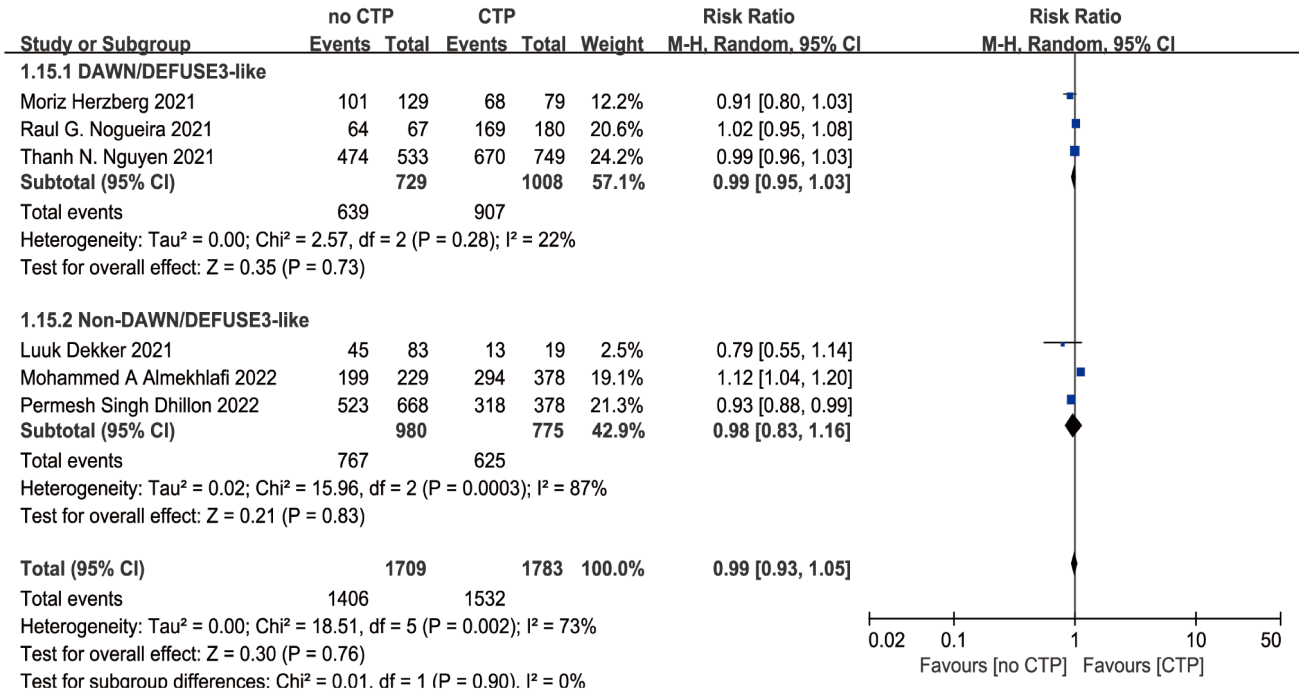

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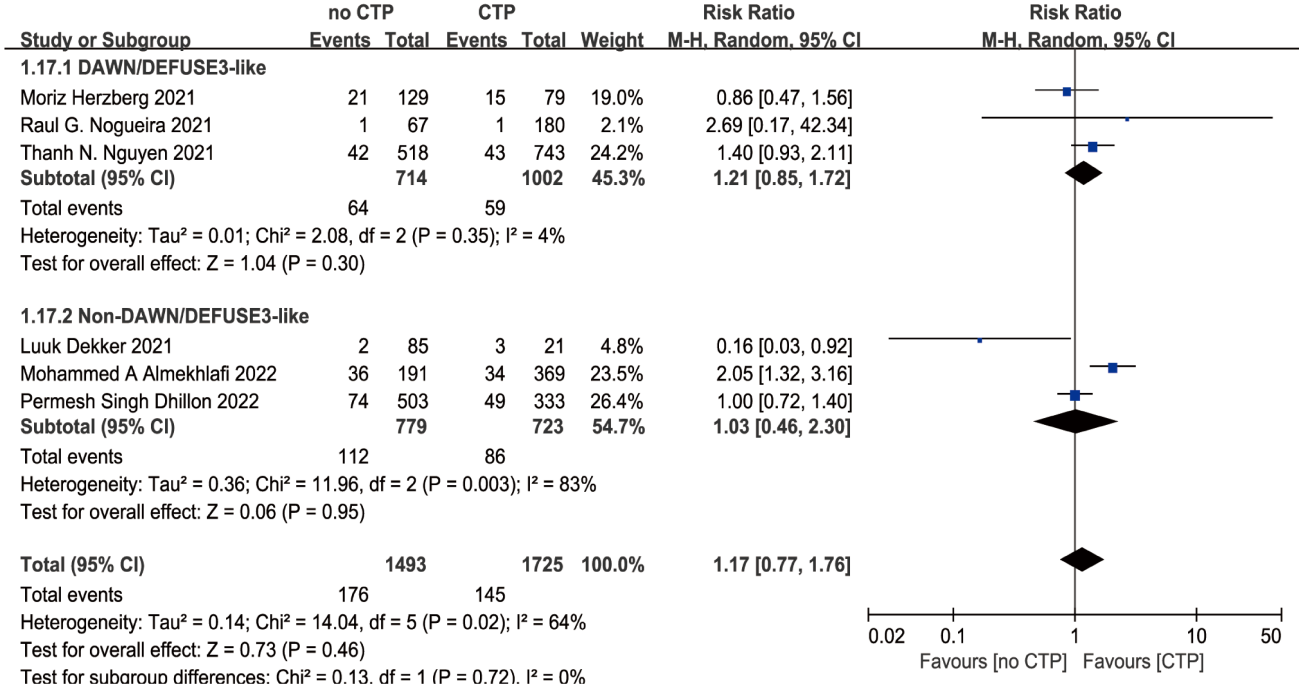

Figure 4 Forest plot of (A) successful recanalization and (B) any intracranial hemorrhage in patients with large vessel occlusion comparing the NCCT±CTA imaging selection modality (no-CTP group) versus the CTP imaging selection modality (CTP group). NCCT, non-contrast CT; CTA, CT angiography; CTP, CT perfusion.

for the detection of ischemia increases over time, potentially resulting in a higher accuracy for irreversible injury than the relative cerebral blood flow,[24] since the presence of clinical core mismatch does not decrease with time.[25] Moreover, a recent analysis of the HERMES cohort (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) suggested no significant interaction between CTP mismatch volume and functional outcomes.[26] It can be supported by evidence that

perfusion imaging overestimates the degree of irreversible brain injury.[27] More importantly, since advanced imaging is not generally available, using NCCT±CTA will be a reasonable option for the extended window. Further evidence is provided by the recent CLEAR study that the clinical benefit of EVT in the extended time window does not necessarily depend on the modality of imaging, but rather on the speed of the successful treatment.[18 28] In the SWIFT PRIME trial, the application of magnetic perfusion resonance imaging did not heighten the effect of EVT, but was connected with potential treatment delays.[29] Of note, the door-to-puncture time was shorter in patients selected by NCCT than in those selected by CTP or MRI. Hence, the simpler, less costly, and easier NCCT±CTA imaging selection modality could be an alternative to the CTP imaging selection modality.

The mortality without CTP selection paradigms in the overall analysis was higher than with CTP. However, the mortality in subgroup analysis was roughly the same between these two imaging selection modalities. In the DAWN/DEFUSE 3-like subgroup, included studies were limited to patients with premorbid mRS scores of 0–2, occlusions of the internal carotid or proximal middle cerebral arteries (M1/M2 segments), and median (IQR) ASPECTS of 8. Considering the safety of the treatment, the ideal candidates for successful EVT selected by NCCT±CTA imaging would be those who meet the DAWN/DEFUSE 3-like criteria. The results of the meta-analyses correspond with the findings from some previous studies.[30] Consequently, the results of this analysis cannot be extrapolated to other populations.

There are some limitations to this meta-analysis. First, all studies included in this meta-analysis are retrospective observational research so there may be selection bias confounding the results. Specifically, given the lack of data on the number of patients excluded from EVT treatment and their outcomes, we could only compare the overall results of patients who ultimately underwent EVT treatment. Furthermore, the explicit criteria used to select eligible patients with AIS-LVO according to the imaging selection modality were unavailable in all the included studies. While the final results were similar, this does not mean that the same patients were selected in or out and all classification methods may be inaccurate. Finally, differentiation of imaging interpretation and post-processing software across the different sites and centers may lead to bias. Only well-conducted prospective randomized controlled trials can accurately evaluate the necessity of CTP for patient selection in EVT. We interpreted the results carefully. Although bias was unavoidable in the analysis, we can conjecture that some patients in the NCCT±CTA imaging group would not have achieved good outcomes if they were not offered EVT. More candidates could be identified using NCCT±CTA imaging for EVT from patients with AIS in the 6–24 hour time window. Similar deductions were found in several studies. The ASTRAL cohort showed that twice as many patients were identified for EVT by applying a more liberal clinical/imaging mismatch criteria than strict trial (DAWN and/or DEFUSE 3) criteria.[15] Another study showed that 18% of trial ineligible patients with AIS-LVO receiving off-label EVT achieved outcomes comparable to DAWN and DEFUSE 3-eligible patients.[16]

Currently, two randomized trials are under way to investigate more simplified imaging selection modalities in the 6–24-hour time windows—namely, the MR CLEAN LATE trial (Endovascular Treatment of Acute Ischemic Stroke in the Netherlands for Late Arrivals; ISRCTN19922220) and the RESILIENT-Extended trial (Randomization of Endovascular Treatment in Acute Ischemic Stroke in the Extended Time Window; NCT04256096). While awaiting the results of more inclusive randomized controlled trials, it is necessary to use a personalized imaging modality to get maximum benefits from EVT for late-presenting patients with AIS-LVO.

CONCLUSIONS

The simplified NCCT±CTA imaging selection modality achieved comparable functional outcomes to those with CTP imaging in the current meta-analysis. The analysis could provide an alternative imaging strategy to EVT for patients with AIS-LVO in the 6–24-hour time window, especially in centers that lack advanced imaging capabilities. While awaiting confirmatory data from well-conducted prospective randomized trials, the current analysis suggests that a net benefit from EVT may still be obtained in patients selected with simplified NCCT±CTA imaging in the extended window.

Contributors Guarantor of integrity of entire study: CQ. Study concept/study design: ZD, SD, JZ, ZY, CQ. Data acquisition: all authors. Data extraction and analysis: ZD, SD, JZ, SC. Manuscript drafting: ZD. Manuscript revision for important intellectual content: all authors. Approval of final version of submitted manuscript: all authors. Statistical analysis: ZD, SD, JZ, LZ. Manuscript editing: all authors. All authors agree to ensure any questions related to the work are appropriately resolved.

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