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SYSTEMATIC REVIEW AND META-ANALYSIS

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Imaging-Based Patient Selection and Endovascular Therapy of Ischemic Stroke

A Stratified Meta-Analysis

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Abstract: The positive results of recent trials for the treatment of acute ischemic stroke have highlighted the importance of imaging selection before endovascular therapy. We performed a stratified meta-analysis to confirm this new understanding.

We searched EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov in April 2015 for randomized controlled trials evaluating the effect of endovascular treatment in patients with acute ischemic stroke. The meta-analysis was stratified by whether computed tomographic angiography (CTA) was used to select patients. Outcome data were pooled using fixed-effects models.

Seven randomized controlled trials with 2217 patients were included in this study. Endovascular therapy significantly increased the rate of 90-day functional independence (a modified Rankin score of 0–2) in patients with a CTA-confirmed large-vessel occlusion (relative risk [RR] = 1.75, 95% confidence interval [CI]: 1.48–2.06, $I^2 = 0.0\%$), and reduced 90-day mortality in patients with occlusion stroke with a small ischemic core (RR = 0.58, 95% CI: 0.37–0.89, $I^2 = 0.0\%$). The functional benefit was significantly greater in patients with CTA-based selection than in those without ($Z = 5.04$, $P < 0.001$). The mortality benefit was significantly greater in patients with a large-vessel occlusion and a small ischemic core than in those without CTA-based selection ($Z = 2.04$, $P = 0.041$). There was no evidence of between-study heterogeneity or publication bias.

This meta-analysis showed the effect of vascular imaging on identifying patients with acute ischemic stroke with a proximal vessel occlusion and a small ischemic core, who would benefit from endovascular therapy.

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Abbreviations: CI = confidence interval, CTA = computed tomographic angiography, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, RR = relative risk, tPA = tissue-type plasminogen activator.

INTRODUCTION

Stroke is the second most common cause of death and the third most common cause of disability worldwide.[1,2] Acute ischemic stroke due to large-vessel occlusion is the most common subtype of stroke.[3] To date, intravenous tissue-type plasminogen activator (tPA) within 4.5 hours after symptom onset has been the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke.[4] However, patients with intracranial large-vessel occlusion are often not responsive to intravenous tPA, and 60–80% of these patients die within 90 days after stroke onset or do not regain functional independence despite intravenous tPA treatment.[5,6] Therefore, new therapies are urgently needed to treat stroke attributable to large-vessel occlusion.

Endovascular therapy using mechanical devices delivered via catheter angiography has been attracting increasing attention, and has been regarded as a potentially important modality in treating patients with large-vessel occlusion. However, the published results of randomized controlled trials (RCTs) have been inconsistent. In 2013, 3 RCTs reported no superiority of endovascular therapy as compared with intravenous tPA alone,[6–8] whereas 4 recent RCTs demonstrated that endovascular therapy significantly improved clinical outcomes in patients with acute ischemic stroke.[5,9–11] A major difference between RCTs with positive results and those with neutral results may lie in the use of computed tomographic angiography (CTA) to select patients with proximal intracranial arterial occlusion.[12] To confirm the significance of brain imaging in identifying patients who would benefit from endovascular therapy, we performed this stratified meta-analysis.

METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] Ethics approval was not necessary for this study, as only de-identified pooled data from individual studies were analyzed.

Data Sources and Search Strategy

A systematic literature search was conducted on April 21, 2015 using EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. We limited our search to RCTs conducted in humans. Details of the search strategy are provided in Table S1, http://links.lww.com/MD/A415. Initially,

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titles alone were reviewed for suitability. The abstracts of suitable titles were obtained, and these were then reviewed with regard to suitability for full-text retrieval. Data were then extracted from suitable full-text reports. Additional appropriate reports were added when discovered by citation tracking.

Study Selection

The main inclusion criterion was an RCT comparing endovascular treatment plus standard care with standard care alone, or comparing endovascular treatment with standard care in adults (aged $\geq$18 yr) with acute ischemic stroke, with clinical outcomes reported. No restrictions on language, follow-up, or study size were applied. We excluded studies in which the control groups did not include intravenous tPA,[14–16] because the latest guidelines recommend that patients with acute ischemic stroke should receive intravenous tPA if eligible (Class I; Level of Evidence A).[17] The results from those trials that did not use intravenous tPA as a control are not directly applicable to current decision making with regard to treatment.

The primary outcome was functional independence (a modified Rankin score of 0–2) at 90 days, and the secondary outcome was 90-day mortality.

Data Extraction and Quality Assessment

Two authors independently extracted data using a predetermined data collection template. In the event of disagreement about study inclusion or interpretation of data, consensus was reached by discussion.

The following data were recorded: publication characteristics, countries or regions of the study, study centers, sample size, patient characteristics, occlusion location, National Institutes of Health Stroke Scale score, onset-to-treatment interval, use of CTA, patient selection based on a small ischemic core, intention-to-treat analysis, and efficacy outcomes.

Study quality was independently assessed by 2 reviewers, who used the Cochrane Collaboration's risk-of-bias method.[18] Supplementary Figure S1, http://links.lww.com/MD/A415 shows the risk of bias of the included trials.

Data Synthesis and Analysis

Pooled relative risk (RR) and 95% confidence interval (CI) were calculated using a fixed-effects model with the Mantel–Haenszel method, given the absence of moderate inconsistency (>50%) across studies. Prespecified sensitivity analyses using a DerSimonian–Laird random-effects model were also conducted. The extent of variability across studies attributable to

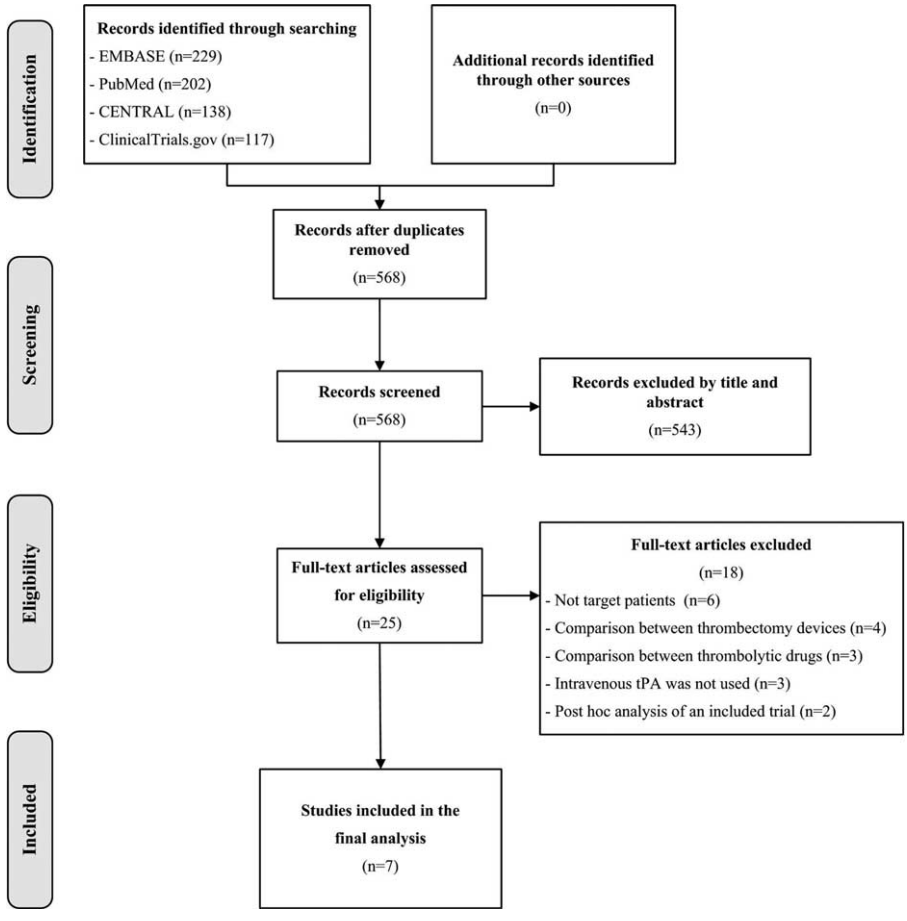

FIGURE 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

heterogeneity beyond chance was estimated using the I^2 statistic. This meta-analysis was stratified by whether CTA was used to select patients, and the 2 pooled RRs were compared using a Z test.[19] Potential publication bias was assessed with the Egger's test and represented graphically with funnel plots of the natural log of the RR versus its standard error.[20] STATA 11 (Stata Corp, College Station, TX) was used for statistical computations. A 2-sided P value of < 0.05 was considered significant.

RESULTS

Study Selection

Figure 1 shows the study selection process. The initial search identified 568 publications. The full text of 25 articles was reviewed in detail, and 18 were further excluded for the following reasons: not targeting patients (n=6), trials comparing effects between thrombectomy devices (n = 4), comparing effects between thrombolytic drugs (n = 3), a control group that did not include intravenous tPA (n = 3), and post-hoc analysis of an included trial (n = 2). Ultimately, 7 RCTs with 2217 participants were included in this meta-analysis (Tables 1 and 2),[5–11] of which 4 trials used CTA to select patients with proximal intracranial arterial occlusion.[5,9–11] Three of the 4 trials further adopted advanced imaging techniques to select patients with a small ischemic core, and either moderate-to-good collateral circulation or salvageable brain tissue.[9-11]

Functional Independence

Figure 2 presents that the rate of functional independence at 90 days was significantly increased with endovascular therapy in patients undergoing CTA-based selection (RR = 1.75, 95% CI: 1.48–2.06, $I^2 = 0.0\%$), but this significance disappeared in patients without CTA-based selection (RR = 0.99, 95% CI: 0.85–1.14, $I^2 = 0.0\%$). The difference between the 2 pooled RRs was significant ($Z = 5.04$, $P < 0.001$).

All-Cause Mortality

As shown in Figure 3, there was no significant effect of endovascular therapy on 90-day mortality, regardless of whether CTA-based selection was used (CTA-based: RR = 0.78, 95% CI: 0.60–1.01, $I^2 = 21.4\%$; non-CTA-based: RR = 0.97, 95% CI: 0.75–1.26, $I^2 = 23.8\%$). However, when restricted to the 3 trials including patients with a small ischemic core, the meta-analysis showed a significant mortality benefit with endovascular therapy (Figure 4; RR = 0.58, 95% CI: 0.37–0.89, $I^2 = 0.0\%$). The pooled RR for mortality derived from patients with a small infarct core was significantly lower than that derived from patients without CTA-based selection ($Z = 2.04$, $P = 0.041$).

Sensitivity Analysis and Publication Bias

The results of sensitivity analyses using random-effects models were highly consistent with the main findings from fixed-effects models, and are displayed in the Supplementary Figures S2–S4, http://links.lww.com/MD/A415.

There was no evidence of publication bias on the basis of either visual inspection of the funnel plots (Figures 5 and 6) or Egger's test for the primary outcome ($P = 0.788$ for non-CTA-based trials and $P = 0.926$ for CTA-based trials, respectively)

TABLE 1. Baseline Characteristics of Included Trials

Trial	Country, Centers	Sample Size	Male,%	Mean Age, Y	Occlusion Location	NIHSS Score, IQR	Onset to IV tPA, Min*	Onset to EVT, H	CTA	Small Ischemic Core
ESCAPE[10] 2015	Worldwide, 22	315	52	71 (median)	MCA with or without ICA	12–20	110/125 (median)	<12	Yes	Yes
EXTEND-IA[9] 2015	AUS and NZ, 10	70	49	69	M1, M2, ICA	9–20	127/145 (median)	<6	Yes	Yes
IMS III[6] 2013	Worldwide, 58	656	58	69 (median)	M1, ICA, BA	2–26 (range)	122/121 (mean)	<5	No	No
MR CLEAN[5] 2015	Netherlands, 16	500	58	66	ICA, M1, M2, A1, A2	14–22	85/87 (median)	<6	Yes	No
MR RESCUE[8] 2013	North America, 22	118	48	66	ICA, M1, M2	13–21	NS	<8	No	No
SWIFT PRIME[11] 2015	Worldwide, 39	196	51	66	ICA, M1	13–20	111/117 (median)	<6	Yes	Yes
SYNTHESIS Expansion[7] 2013	Italy, NS	362	58	67	NS	9–18	NS	<6	No	No

A1 = A1 segment of the anterior cerebral artery; A2 = A2 segment of the anterior cerebral artery; BA = basilar artery; CTA = computed tomographic angiography; EVT = endovascular therapy; ICA = internal carotid artery; IV tPA = intravenous tissue-type plasminogen activator; MCA = middle cerebral artery; M1 = the first segment of the middle cerebral artery; M2 = the second segment of the middle cerebral artery; NIHSS indicates National Institutes of Health Stroke Scale; NS = not specified.

*Intervention group/control group.

TABLE 2. Primary and Secondary Outcomes of Included Trials

				Outcomes at 90 Days			
		Treatment		Functional Independence		Death	
Trial	ITT	Intervention	Control	Intervention	Control	Intervention	Control
ESCAPE[10] 2015	Yes	Retrievable stents (most were Solitaire stents) plus standard care (72.7% of patients received IV tPA)	Standard care (78.7% received IV tPA)	87/164	43/147	17/164	28/147
EXTEND-IA[9] 2015	Yes	Solitaire FR retrievable stents plus IV tPA (0.9 mg/kg)	IV tPA (0.9 mg/kg)	25/35	14/35	3/35	7/35
IMS III[6] 2013	Yes	(Merci retriever, Penumbra system, Solitaire FR revascularization device, or intraarterial tPA) plus IV tPA: 0.9 mg/kg (maximum: 90 mg)	IV tPA: 0.9 mg/kg (maximum: 90 mg)	177/434	86/222	83/434	48/222
MR CLEAN[5] 2015	Yes	Retrievable stents or intraarterial thrombolytic agents plus usual care (87.1% received IV tPA)	Usual care (90.6% received IV tPA)	76/233	51/267	49/233	59/267
MR RESCUE[8] 2013	NS	(Merci retriever, Penumbra system, or intraarterial tPA) plus standard care (43.8% received IV tPA)	Standard care (29.6% received IV tPA)	12/64	11/54	12/64	13/54
SWIFT PRIME[11] 2015	Yes	(Solitaire FR or Solitaire 2 device) plus IV tPA (dose was NS)	IV tPA (dose was NS)	59/98	33/93	9/98	12/97
SYNTHESIS Expansion[7] 2013	Yes	Intraarterial tPA, devices (Solitaire, Penumbra, Trevo, Merci), or both	IV tPA: 0.9 mg/kg (maximum: 90 mg)	76/181	84/181	26/181	18/181

ITT indicates intention-to-treat; IV tPA = intravenous tissue-type plasminogen activator; NS = not specified.

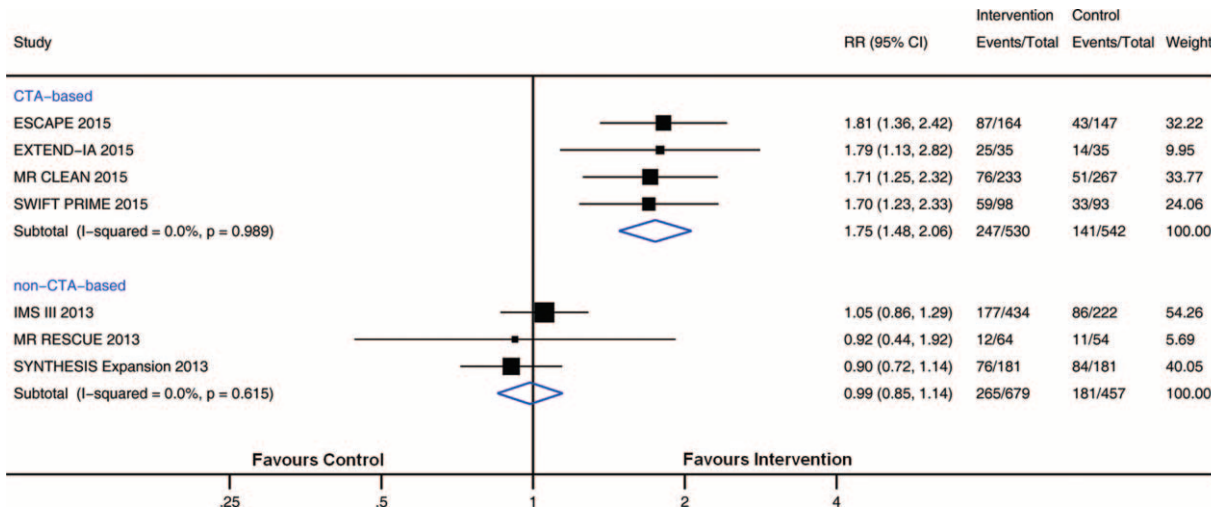

FIGURE 2. Fixed-effects model. Meta-analysis of the effect of endovascular therapy on functional independence at 90 days, stratified by whether computed tomographic angiography (CTA) was used to select patients.

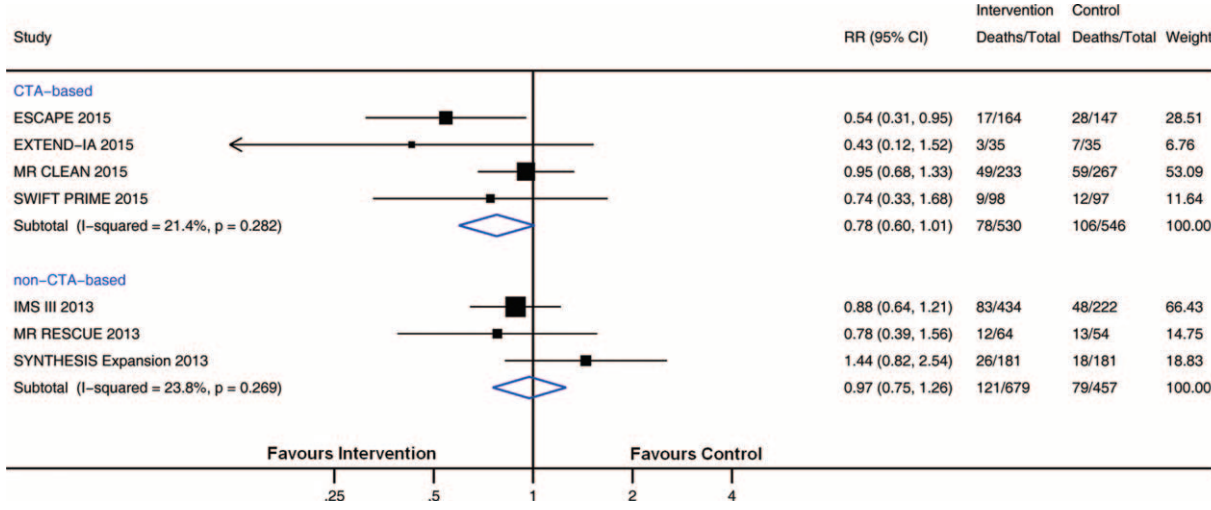

FIGURE 3. Fixed-effects model. Meta-analysis of the effect of endovascular therapy on 90-day mortality, stratified by whether computed tomographic angiography (CTA) was used to select patients.

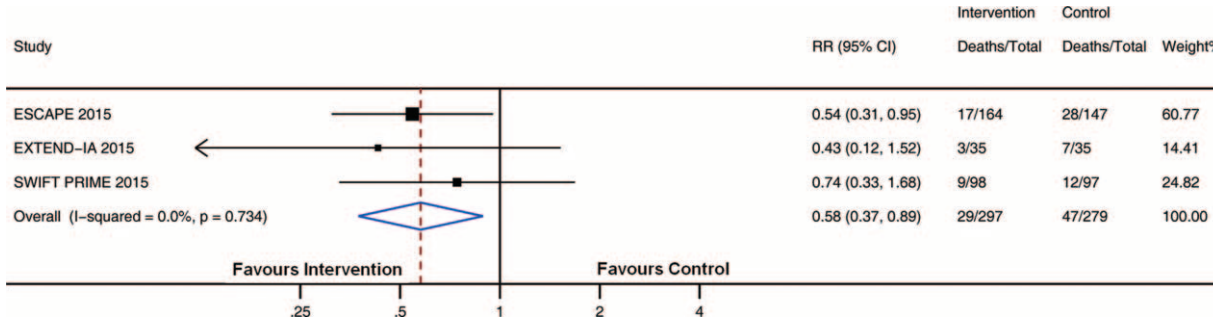

FIGURE 4. Fixed-effects model. Meta-analysis of the effect of endovascular therapy on 90-day mortality in patients with acute ischemic stroke with a proximal vessel occlusion and a small ischemic core.

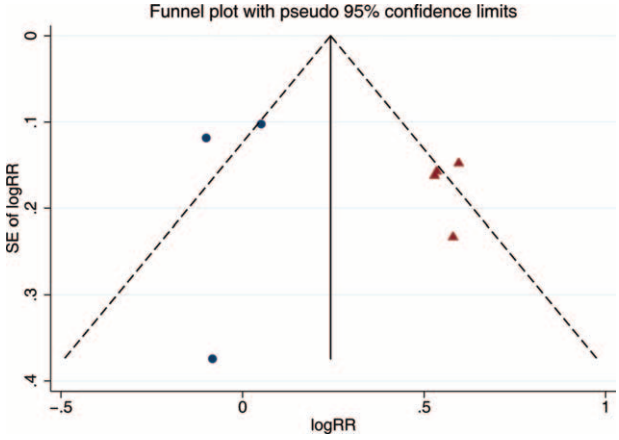

FIGURE 5. Funnel plot for studies evaluating the effect of endovascular therapy on functional independence at 90 days, stratified by whether computed tomographic angiography (CTA) was used to select patients. Circles indicate the trials without CTA-based selection; triangles indicate the trials with CTA-based selection. There was no evidence of publication bias.

and secondary outcome ($P = 0.794$ for non-CTA-based trials and $P = 0.234$ for CTA-based trials, respectively).

DISCUSSION

Our main findings were: endovascular therapy significantly increased the rate of functional independence in patients with a CTA-confirmed large-vessel occlusion, and reduced mortality in patients with occlusion stroke with a small ischemic core; the functional benefit was significantly greater in patients with CTA-based selection, and the mortality benefit was significantly greater in patients with a CTA-confirmed large-vessel occlusion and a small ischemic core than in those without CTA-based selection.

Previous RCTs have identified the efficacy of the use of intravenous tPA administered up to 4.5 hours after the onset of symptoms of acute ischemic stroke.[21,22] However, the limitations of this therapy, including the narrow therapeutic time window and over numerous contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage, also have been well recognized.[17] Additionally, intravenous tPA appears to be much less effective, succeeding only about 15 to 25% of the time,[23] in recanalizing more proximal occlusions of the major intracranial arteries.[24] Therefore, endovascular therapy has been attracting increasing attention in recent years. Endovascular treatment consists of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The first positive trial of endovascular therapy was the PROACT II study involving patients with angiographically visualized occlusion of the middle cerebral artery, which found that treatment with intraarterial recombinant prourokinase within 6 hours of onset significantly increased the rate of functional independence at 90 days.[14] Unfortunately, the subsequent trials did not verify this clinical benefit even with the addition of first-generation thrombectomy devices.[6–8] The crucial knowledge learned from these failed trials is the need for the proof of a large-vessel occlusion and a small infarct core.[25,26] Consequently, the 4 more recently presented trials, all of which were successful, used CTA to identify an occlusion amenable to endovascular therapy as an appropriate prerequisite for inclusion.[5,9–11] The data presented in this study support the importance of imaging-based selection and emphasize the urgent need to establish a standardized imaging protocol for patient selection.

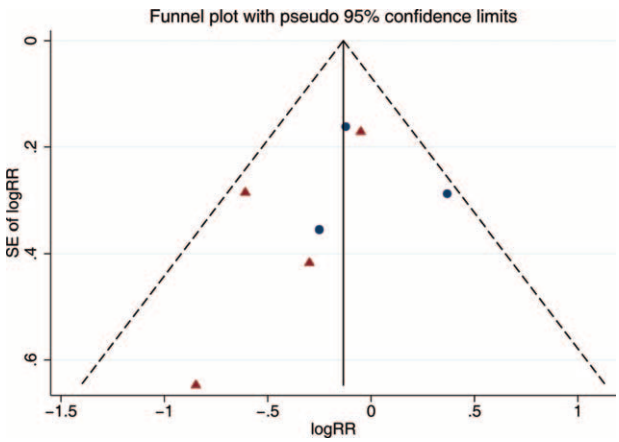

FIGURE 6. Funnel plot for studies evaluating the effect of endovascular therapy on 90-day mortality, stratified by whether computed tomographic angiography (CTA) was used to select patients. Circles indicate the trials without CTA-based selection; triangles indicate the trials with CTA-based selection. There was no evidence of publication bias.

There is a strong consensus among neurointerventionists that ''time is brain.'' Device technology is advancing quickly, and computed tomographic perfusion imaging can now be rapidly performed and indicate the extent of irreversibly injured brain in the ischemic core and potentially salvageable.[9,11] This study showed a significant mortality benefit with endovascular therapy in patients with a small infarct core, which indicates that the future selective imaging workflow for endovascular therapy should exclude patients with a large area of irreversibly injured infarct core.

The major advantages of this meta-analysis are the inclusion of high-quality RCTs, larger sample sizes, robust results from sensitivity analysis, no significant between-study heterogeneity, and no evidence of publication bias. However, our study also has some limitations. First, the pooled RRs were calculated using trial-level rather than individual-level data. Individual patient information would have added further insights into the analysis. Second, only 7 trials were included, which might undermine the strength of our findings. Third, as with any meta-analyses, publication bias remains a threat to the validity of our results. Fourth, most patients included in the RCTs were Caucasians. Hence, generalizing the effect of endovascular therapy to other groups can be challenging, especially the East Asian population, as the prevalence of intracranial atherosclerosis and the risk of hemorrhagic transformation is higher in this cohort.[27] We propose that Asian investigators conduct multinational collaborative trials to evaluate the effect of endovascular therapy and determine the optimal treatment protocol for Asian patients with acute ischemic stroke. Finally, the difference in functional and mortality benefit of endovascular therapy observed in this study may be attributed to the use of new devices in recent trials.

In conclusion, our meta-analysis showed the effect of vascular imaging on identifying patients with acute ischemic stroke with a proximal vessel occlusion and a small ischemic core who would benefit from endovascular therapy.

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