Comparison of Four Food and Drug Administration–Approved Mechanical Thrombectomy Devices for Acute Ischemic Stroke: A Network Meta-Analysis

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■ BACKGROUND: **The use of mechanical thrombectomy for the treatment of acute ischemic stroke (AIS) is rapidly increasing. However, there are limited data on the comparative effects of the various devices approved by the U.S. Food and Drug Administration for the treatment of AIS. We aimed to perform a network meta-analysis to assess the relative efficacy and safety of 4 thrombectomy devices.**

■ METHODS: **We searched PubMed, the Cochrane Library Central Register of Controlled Trials, and Embase for randomized controlled trials (RCTs) and parallel group observational studies that assessed thrombectomy devices in patients with AIS. Primary efficacy outcomes included functional independence (90-day modified Rankin Scale score) and recanalization rate (thrombolysis in cerebral infarction score). Safety outcomes included incidence of symptomatic intracranial hemorrhages and 90-day mortality.**

■ RESULTS: **Five RCTs and 5 observational studies, including 1659 participants, were included. According to GRADE (Grading of Recommendations, Assessment, Development and Evaluations), most of the studies are of moderate quality of evidence. Compared with Penumbra, Solitaire and Trevo were associated with higher rates of functional independence (3.75 [1.44–7.66] and 4.68 [1.42–11.50], respectively). For revascularization, Solitaire and Trevo had higher rates of successful recanalization than Merci (2.99 [1.15–6.53] and 3.34 [1.20–8.01], respectively). In terms of safety outcomes (symptomatic intracerebral hemorrhage and mortality), there was no significant difference between any comparators.**

■ CONCLUSIONS: **We concluded that stent retriever devices were superior to non–stent retriever devices in functional outcomes and recanalization without significant increases in death or symptomatic hemorrhage. We found no evidence for a differential therapy effect by stent type. Further high-quality RCTs assessing efficacy difference between these 2 stent retrievers are justified.**

INTRODUCTION

Stroke is the one of the leading causes of morbidity and mortality worldwide. Timely reperfusion with intravenous (IV) tissue plasminogen activator (t-PA) is widely used as a standard treatment for acute ischemic stroke (AIS).[1] However, as a consequence of the narrow therapeutic window, certain contraindications, and low recanalization rates, the administration of IV t-PA was limited.[2] This factor prompted a substantial evolution in endovascular therapy, shifting from intra-arterial thrombolysis with t-PA to modern mechanical thrombectomy techniques.

Studies showed benefits for mechanical thrombectomy in terms of higher recanalization rates,[3-8] with extensive use in patients with AIS across a wide range of age and baseline stroke severity,[9] enabling a safe procedure for patients with contraindications to t-PA as a result of timing or bleeding risk. Recent positive trials showing substantial efficacy of mechanical thrombectomy[5-7] have led to a rapid increase in the use of the treatment. Four

Key words
- Acute ischemic stroke
- Mechanical thrombectomy devices
- Network meta-analysis

Abbreviations and Acronyms
AIS: Acute ischemic stroke
CI: Confidence interval
IV: Intravenous
mRS: Modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
NMA: Network meta-analysis
NOS: Newcastle-Ottawa Scale
OR: Odds ratio
RCT: Randomized controlled trial
sICH: Symptomatic intracerebral hemorrhage
TICI: Thrombolysis in cerebral infarction
t-PA: Tissue plasminogen activator

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mechanical thrombectomy devices have been approved by the U.S. Food and Drug Administration for the treatment of AIS within 8 hours onset as the sole therapy or in combination with t-PA.[10] These devices include the first-generation Merci Retriever System and Penumbra System, as well as the second-generation (the newer stent retrievers) Solitaire FR Device and Trevo Retriever. These devices differ in shape, size, and physical appearance.[11] Several studies have shown the superiority of stent retrievers over other thrombectomy devices.[5,6,12] However, we are not aware of any studies directly comparing the efficacy and safety of the 4 approved thrombectomy devices or of direct randomized head-to-head trials. The choice of the type of device is therefore at the discretion of physicians, relying on their experience.

We therefore aimed to perform a network meta-analysis (NMA) using both direct and indirect evidence to systematically assess and rank the effectiveness and safety of these 4 devices in the treatment of AIS.

METHODS

This systematic review conformed to principles outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement extension for NMA[13] (**Appendix 1**).

Search Strategy

To compare the efficacy and safety of different thrombectomy devices, we captured randomized controlled trials (RCTs) and observational studies published in English up to February 1, 2018, compiled from the major online databases PubMed, Embase, and the Cochrane Library Central Register of Controlled Trials. The search was executed using a combination of MeSH (Medical Subject Heading) terms (e.g., 'thrombectomy,' 'stroke,' or 'stent') and/or the free-text key words (e.g., stent*, retriev*, Merci, Penumbra, Solitaire, Trevo, or Revive). In addition, we screened by hand the references of retrieved studies and relevant systematic reviews. The details of modified search algorithm are shown in **Appendix 2**.

Study Selection

Studies were captured for inclusion if they were prospective RCTs or observational studies, assessing endovascular therapy using modern mechanical thrombectomy devices (devices alone or in conjunction with IV t-PA or intra-arterial t-PA) in adult patients with AIS. The intervention arms of our NMA included the following 4 mechanical thrombectomy devices: Merci Retriever, Penumbra System devices, Solitaire Flow Restoration Device, and Trevo Retriever. Usual care alone and IV t-PA (when eligible) were regarded together as a single control arm, whereas the intra-arterial t-PA arm was regarded as another control arm. For studies concerning multiple publications, data from the most complete publication or the most recent were included in our analysis.

Studies were excluded if data were unavailable for any of these outcomes (modified Rankin Scale [mRS] score; recanalization rates; symptomatic intracerebral hemorrhage [sICH]; mortality) and if they did not describe which specific device was used as the thrombectomy group. Pilot studies and post hoc analyses were also excluded. We did not search the gray literature for unpublished records, such as conference abstracts, because of incomplete or insufficient data.

Two investigators (L.H.D. and S.Q.) independently scanned titles and abstracts of concerned references to evaluate potential relevant eligibility. Articles that advanced beyond initial scanning were retrieved in full text and then reviewed by 2 investigators (L.H.D. and S.Q.) independently to identify eligibility for NMA. Discrepancies were resolved by discussion.

Outcomes

Primary outcome measures included clinical outcomes (assessed by mRS score at 90 days) and vessel patency outcomes (assessed by the thrombolysis in cerebral infarction [TICI] score). For the clinical outcome, favorable outcome was an mRS score of 0–2, which indicates functional independence. Efficacy outcome was evaluated by the degree of revascularization, and successful recanalization was defined as thrombolysis in TICI flow $\geq$2b at the end of the endovascular routine, corresponding to reperfusion of >50% of the occlusion territory.

Safety outcomes included 1) the proportion of patients with sICHs, defined as any intracerebral hemorrhage within 24 hours related to a worsening of $\leq$4 points on the National Institutes of Health Stroke Scale (NIHSS) or which resulted in death, and 2) all-cause mortality at 90 days.

For all these outcomes, number of events and patients in each arm were collected.

Data Extraction and Statistical Analysis

For each study chosen for inclusion, data of study and patient characteristics were extracted independently (L.H.D. and S.Q.) using a pilot-tested standardized form. Discrepancies were resolved by consensus with the third author (M.L.).

Pairwise meta-analysis applying random-effects model was performed first.[14] We estimated the relative effect of the competing treatment through the application of odds ratio (OR) for dichotomous outcomes, with 95% confidence interval (CI). The statistical heterogeneity among studies was assessed by the I^2 statistic and the Cochran Q test. I^2 >50% or P $\leq$ 0.05 for the Q test indicates remarkable study heterogeneity.

We conducted random-effects Bayesian NMA for indirect comparisons using the Markov chain Monte Carlo method in WinBUGS version 1.4.3 (Biostatistics the Medical Research Council, Cambridge, United Kingdom).[15-17] The effect sizes and their credible intervals were summarized. We estimated the relative ranking probability of each strategy and obtained the hierarchy of competing interventions using rankgrams and SUCRA (surface under the cumulative ranking curve). We used the node-splitting method to check for inconsistency, excluding 1 direct comparison at a time and estimating the indirect effect for the excluded comparison.[18]

Risk of Bias and Quality of Evidence

We elucidated the risk of selection bias, information bias, and bias in the analysis using the Cochrane Collaboration Handbook.[14] We used a funnel plot to detect publication bias. We applied GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology to assess the quality of the result derived from NMA.[19] Direct evidence from studies starts at high quality and can be downgraded based on relevant risks.[19]

We assessed the quality of each conventional study using the Newcastle-Ottawa Scale (NOS).[20] It offers capacity in evaluating

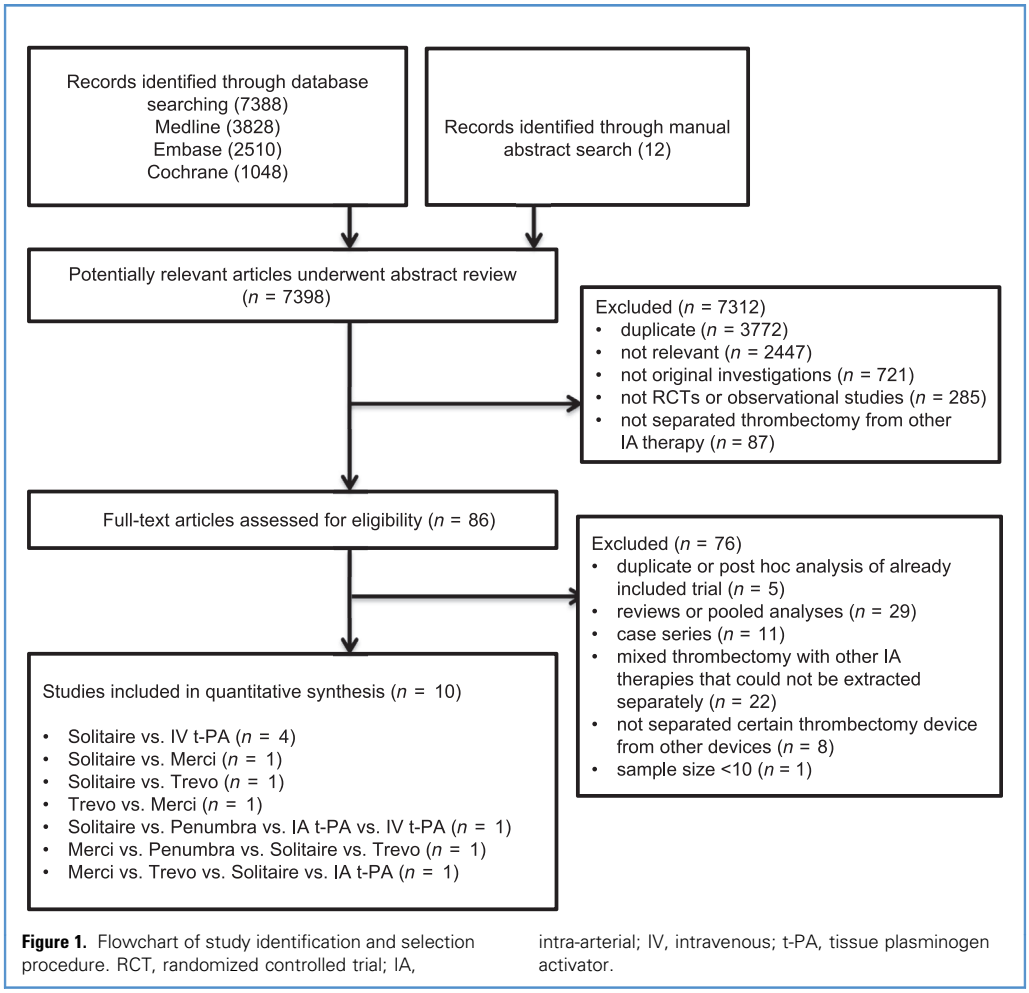

Figure 1. Flowchart of study identification and selection procedure. RCT, randomized controlled trial; IA, intra-arterial; IV, intravenous; t-PA, tissue plasminogen activator.

cohort studies by 8 items with 3 major parts, including the study population selection (selection), comparability (comparability), and result (outcome). The NOS uses the semi-quantitative principles of a star system to perform quality assessment and a full score is 9 stars. All quality assessment was performed by 2 independent reviewers (L.H.D. and S.Q.). When there were different outcomes, the 2 reviewers resolved the discrepancy in the results through discussion.

RESULTS

Search and Selection

The literature search yielded 7398 articles, as shown in the PRISMA flowchart (**Appendix 1**). Using the search algorithm, we identified 5 RCTs[5,6,21-23] and 5 observational studies,[10,12,24-26] including 1659 participants, which were included in our NMA (**Figure 1**, **Table 1**, and **Appendix 2**).

Study and Patient Characteristics

Publication dates ranged from May 2012 to February 2016, comparing 4 devices. The studies were conducted in various countries. The number of patients allocated to each arm ranged between 5 and 141. Seven studies were 2 arm and 3 were 4 arm. Solitaire and IV t-PA are the 2 most frequent comparators. The Solitaire stent retriever was assessed in 9 studies (n = 1481), Trevo in 4 (n = 692), Merci in 4 (n = 772), and Penumbra in 2 (n = 457). **Figure 2** and **Appendix 4** show the available direct comparisons and network of studies. For the primary clinical outcome, 13 of 15 pairwise comparisons had direct evidence. Four studies recruited patients within 8 hours after symptom onset, whereas in the remainder, the intervals were within 4.5 hours (2 studies, 20%), 6 hours (1 study, 10%), 12 hours (1 study, 10%), and unclear (2 studies, 20%), respectively. The mean/median interval time from symptom onset to arterial puncture of thrombectomy device groups ranged from 146.7 minutes to 434.4 minutes (7.24 hours). Studies were mostly multicenter studies (70%). The range of patient mean age varied from 62.7 to 72.0 years. Of participants, 56.0% were male, and in most studies, the gender was comparable, except in Jang et al.'s study,[26] in which the proportion of males was as high as 80.3%. The mean/median baseline NIHSS score ranged from 11.6 to 19.0, except in Leker et al.'s study,[25] in which the baseline NIHSS of IV t-PA group was 6.4 ± 5.3. More detailed description of studies and treatments is given in **Table 1** and **Appendix 3**.

Table 1. Characteristics of Included Patients for Randomized Controlled Trials

Study	Number of Patients	Intervention/ Control (N)	IV t-PA, N (%)	Age (mean ± SD)	Gender, n (%, male)	Baseline National Institutes of Health Stroke Scale, Median (IQR)/Mean ± SD	Occlusion Site Middle Cerebral Artery, n (%)	Symptom Onset to Arterial Puncture	Alberta Stroke Program Early CT Score (IQR)	Median Glucose Level at Hospital Arrival, Median (IQR)/Mean ± SD/mmol/L	Hypertension, n (%)	Diabetes, n (%)	Atrial Fibrillation, n (%)
Campbell et al., 2015[21]	70	Solitaire (35)	35 (100)	68.6 ± 12.3	17 (49)	17 (13–20)	M1-MCA 20 (57) M2-MCA 4 (11)	210 (83–159) minutes	NR	7.1 ± 2.5	21 (60)	2 (6)	12 (34)
		IV t-PA (35)	35 (100)	70.2 ± 11.8	17 (49)	13 (9–19)	M1-MCA 18 (51) M2-MCA 6 (17)	NR	NR	7.6 ± 3.6	23 (66)	8 (23)	11 (31)
Saver et al., 2015[22]	196	Solitaire (98)	98 (100)	65.0 ± 12.5	54 (55)	17 (13–19)	M1-MCA 62 (67) M2-MCA 13 (14)	224 (165–275) minutes	9 (7–10)	131 ± 46	66/98 (67)	12/98 (12)	35/98 (36)
		IV t-PA (98)	98 (100)	66.3 ± 11.3	45 (47)	17 (13–20)	M1-MCA 72 (77) M2-MCA 6 (6)	NR	9 (8–10)	131 ± 47	35/98 (36)	15/97 (15)	38/97 (39)
Jovin et al., 2015[23]	206	Solitaire (103)	70 (68)	65.7 ± 11.3	55 (53.4)	17.0 (14.0–20.0)	M1-MCA 92 (90.2) M2-MCA 10 (9.8)	269 (201–340) minutes	7 (6–9)	6.8 (5.9–7.9)	62 (60.2)	22 (21.4)	35(34)
		IV t-PA (103)	80 (77.7)	67.2 ± 9.5	54 (52.4)	17.0 (12.0–19.0)	M1-MCA 92 (91.1) M2-MCA 8 (7.9)	NR	8 (6–9)	6.8 (5.9–7.9)	72 (69.9)	19 (18.4)	37 (36)
Saver et al., 2012[5]	113	Solitaire (58)	33%	67.1 ± 12.0	28 (48)	18.0 (9.0–28.0)	M1-MCA 38 (66) M2-MCA 6 (10)	293.5 ± 85.6 minutes	NR	NR	72%	24%	45%
		Merci (55)	47%	67.1 ± 11.1	28 (51)	18.0 (8.0–26.0)	M1-MCA 28 (51) M2-MCA 10 (19)	319.9 ± 88.1 minutes	NR	NR	69%	31%	67%
Nogueira et al., 2012[6]	178	Trevo (88)	51 (58)	67.4 ± 13.9	40 (45)	19.0 (14.0–21.3)	M1-MCA 53 (60) M2-MCA 14 (16)	4.7 (3.5–5.7) hours	NR	127 (105–158)	67 (76)	33 (38)	42 (48)
		Merci (90)	45 (50)	67.0 ± 14.7	36 (40)	18.0 (15.0–21.0)	M1-MCA 55 (61) M2-MCA 13 (14)	4.2 (3.4–5.4) hours	NR	117 (102–143)	74 (82)	23 (26)	38 (42)

Jang et al., 2014[26]	294	Penumbra (25)	NR	67.2 ± 1.0	101 (87.1)	14 (7—18)	MCA 15 (60)	146.7 ± 172.0 minutes	NR	NR	208 (67.8)	77 (25.1)	176 (57.3)
		Solitaire (78)	NR			16 (10—20)	MCA 50 (64)		NR	NR			
		IA t-PA (50)	NR	69.3 ± 10.8	42 (84)	16 (10—21)	MCA 26 (52)	149.2 ± 194.2 minutes	NR	NR			
		IV t-PA (141)	NR	70.2 ± 12.4	93 (66)	12 (7.17.5)	MCA 96 (68)	NR	NR	NR			
Hentschel et al., 2017[10]	166	Merci (30)	11 (36.67)	66.36 ± 13.66	14 (46.67)	18.01 ± 6.35	MCA 21 (70.0)	6.71 ± 4.22 hours	NR	NR	25 (83.33)	10 (33.33)	8 (26.67)
		Penumbra (69)	31 (44.93)	66.09 ± 15.16	32 (46.38)		MCA 38 (55.1)	7.24 ± 5.35 hours	NR	NR	60 (86.96)	21 (30.43)	31 (44.93)
		Solitaire (62)	35 (52.24)	62.66 ± 16.50	33 (49.25)	16.41 ± 6.59	MCA 43 (64.2)	6.91 ± 3.96 hours	NR	NR	55 (82.09)	17 (25.37)	26 (35.82)
		Trevo (5)											
Ribo et al., 2013[12]	315	Merci (119)	40.20%	69 ± 13	NR	17 (12—21)	M2-MCA 8 (6.7)	261 ± 102 minutes	NR	155 ± 65	77.40%	23.70%	47.80%
		Trevo (26)	58.50%	72 ± 13	NR	18 (17—20)	M2-MCA 6 (8.9)	246 ± 82 minutes	NR	127 ± 39	63.50%	20.60%	41.30%
		Solitaire (43)											
		IA t-PA (127)	62.70%	71 ± 12	NR	19 (16—21)	M2-MCA 8 (6.3)	237 ± 81 minutes	NR	138 ± 45	68.90%	19.70%	46.30%
Leker et al., 2012[25]	88	Solitaire (22)	0%	64.7 ± 15.6	11 (50)	11.6 ± 5.7	MCA 22 (100)	NR	NR	NR	15 (68)	5 (23)	10 (45)
		IV t-PA (66)	100%	71.0 ± 14.3	34 (52)	6.4 ± 5.3	MCA 66 (100)	NR	NR	NR	34 (52)	16 (24)	27 (41)
Mendonca et al., 2014[24]	33	Trevo (13)	5 (38)	74 ± 9	NR	19 (16—22)	MCA 8 (61)	245 ± 84 minutes	NR	NR	NR	NR	NR
		Solitaire (20)	10 (50)	70 ± 14	NR	17 (16—19)	MCA 11 (55)	274 ± 88 minutes	NR	NR	NR	NR	NR

IV, intravenous; t-PA, tissue plasminogen activator; IA, intra-arterial; IQR, interquartile range; MCA, middle cerebral artery; NR, not reported.

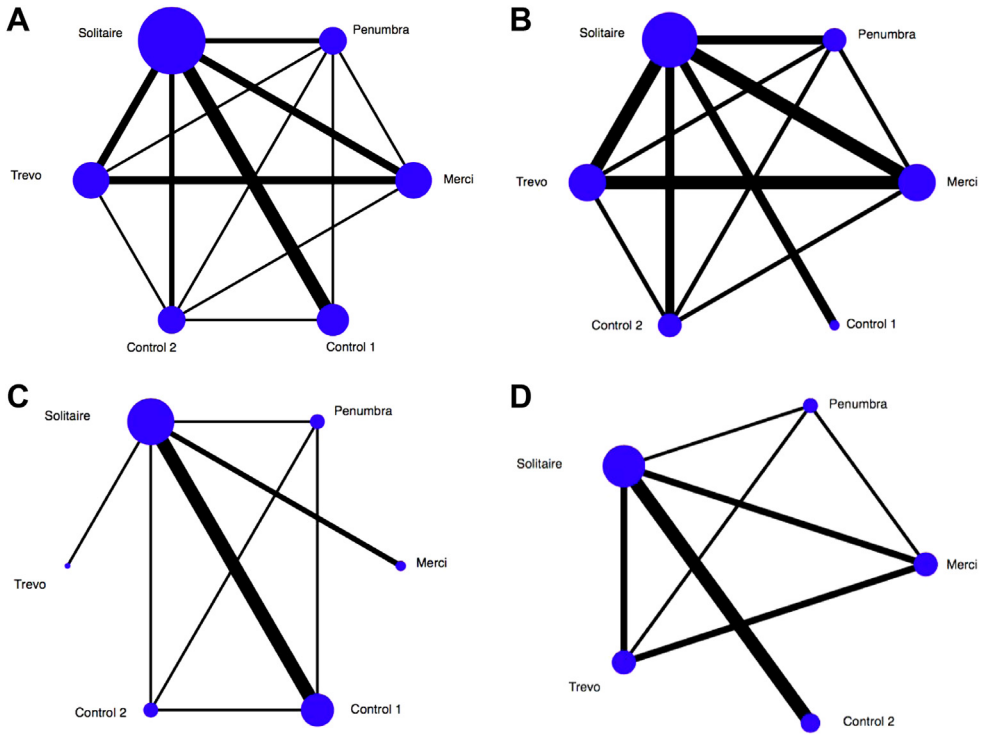

Figure 2. Network of eligible comparisons for primary outcome. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). Control 1, usual care alone and intravenous tissue plasminogen activator (intravenous tissue plasminogen activator) (when eligible); control 2, intra-arterial tissue plasminogen activator (intra-arterial tissue plasminogen activator). (**A**) Network of eligible comparisons for clinical outcomes (assessed by modified Rankin Scale score at 90 days). (**B**) Network of eligible comparisons for vessel patency outcomes (assessed by the thrombolysis in cerebral infarction [TICI] score). (**C**) Network of eligible comparisons for symptomatic intracranial hemorrhages. (**D**) Network of eligible comparisons for all-cause mortality at 90 days.

Quality Assessment and Quality of the Evidence

The methodological quality of involved trials was generally high, with all 5 RCTs using appropriate allocation concealment, randomization procedures, and blinding of outcome assessment. None of the trials used blinding of study participants attributable to the nature of procedure, but they were probably blinded to exactly which device was used. As for risk of bias of the 5 conventional studies, using the NOS tool, 1 study fulfilled all 9 NOS criteria, whereas the remaining 4 studies met 8 criteria. Overall, the quality of included investigations was relatively high. Furthermore, no evidence of small study effects based on funnel plot asymmetry was observed, and the number of studies involved in each arm was relatively small. According to GRADE, the evidence quality of most studies is moderate (Table 2). The networks of individual intervention end points are shown in Appendix 3. There was no inconsistency in the NMA estimates (Appendix 5).

Pairwise and Network Result

Results of direct pairwise meta-analysis are summarized in the Appendix 6. For clinical outcomes, Solitaire was associated with higher rates of good functional outcomes (mRS score 0–2 at 90 days) than were Penumbra and IV t-PA (OR, 2.12; 95% CI, 1.16–3.85; OR 1.41; 95% CI, 1.07–1.84). Trevo had higher rates of good functional outcomes than did Merci (OR, 1.62; 95% CI, 1.02–2.57). For efficacy outcomes, Solitaire had higher rates of successful recanalization (TICI scores 2b–3) than did IV t-PA (OR, 2.11; 95% CI, 1.30–3.42) (Table 2).

The results of the NMA for our primary outcome are shown in Table 2. Solitaire and Trevo ranked as the best 2 for functional independence. Compared with Penumbra, Solitaire and Trevo were associated with higher rates of functional independence (mRS score 0–2 at 90 days) (OR, 3.75; 95% Crl, 1.44–7.66; OR, 4.68; 95% Crl, 1.42–11.50). According to SUCRA, in terms of functional recovery, the most effective procedures for AIS were Trevo (92% probability) and Solitaire (85% probability). We also observed that the use of Solitaire and Trevo increased the odds of favorable outcomes, compared with IV t-PA (OR, 2.49; 95% Crl, 1.50–4.58; OR, 2.77; 95% Crl, 1.17–7.95).

For revascularization efficacy outcome, Solitaire and Trevo had higher rates of successful recanalization than did Merci (OR, 2.99; 95% Crl, 1.15–6.53; OR, 3.34; 95% Crl, 1.20–8.01). Solitaire, Trevo, and Merci were significantly more effective compared with

Table 2. Summary Effect Size of Pairwise and Network Meta-Analysis

Comparisons	Number. of Trials	Pairwise Meta-Analysis Mean Difference/Odds Ratio (95% Confidence Interval)	*P* Value	Heterogeneity I^2	Network Meta-Analysis Mean Difference/Odds Ratios (95% Credible Interval)	Quality of Evidence	Downgraded Reason
Clinical functional outcomes							
Solitaire versus Penumbra	2	**2.12 (1.16–3.85)**	0.02	5.39	**3.75 (1.44–7.66)**	Moderate	Heterogeneity
Trevo versus Penumbra	1	NA	NA	NA	**4.68 (1.42–11.50)**	Low	Imprecision and indirectness
Solitaire versus Control 1	5	**1.41 (1.07–1.84)**	0.42	3.91	**2.49 (1.50–4.58)**	High	-
Trevo versus Control 1	0	NA	NA	NA	**2.77 (1.17–7.95)**	Low	Imprecision and indirectness
Revascularization efficacy outcomes							
Solitaire versus Merci	3	1.42 (1.00–2.03)	0.30	2.4	**2.99 (1.15–6.53)**	Moderate	Imprecision
Trevo versus Merci	3	1.39 (0.95–2.04)	2.04	0.36	**3.34 (1.20–8.01)**	Moderate	Imprecision
Solitaire versus Penumbra	2	1.15 (0.75–1.72)	0.66	0.20	**3.57 (1.01–9.51)**	Moderate	Imprecision
Solitaire versus Control 1	2	**2.11 (1.30–3.42)**	0.02	0.89	**9.53 (3.54–37.74)**	Moderate	Heterogeneity
Trevo versus Control 1	0	NA	NA	NA	**9.10 (2.73–74.63)**	Low	Imprecision and indirectness
Merci versus Control 1	0	NA	NA	NA	**3.15 (1.01–20.16)**	Low	Imprecision and indirectness

Results are expressed as odds ratios with 95% confidence interval or 95% credible interval for dichotomous variables (response). The mean difference with 95% confidence interval or 95% credible interval was used for continuous outcomes. Significant results are in bold. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) was carried out to evaluate the evidence quality of estimates derived from NMA. In this approach, direct evidence from studies starts at high quality and can be downgraded based on risk of bias, imprecision, indirectness, inconsistency (or heterogeneity) and publication bias to levels of moderate, low, and relatively low quality.

NA, not applicable.

IV t-PA (OR, 9.53; 95% CrI, 3.54–37.74; OR, 9.10; 95% CrI, 2.73–74.63; OR, 3.15; 95% CrI, 1.00–20.16). Moreover, Solitaire had higher recanalization rates than did Penumbra (OR, 3.57; 95% CrI, 1.01–9.51). In terms of safety outcomes (sICH and mortality), there was no remarkable difference between any comparators.

DISCUSSION

To our knowledge, this is the first NMA to investigate the differences in clinical outcome, reperfusion, and safety according to thrombectomy device type. Using rigorous NMA methods, we used both direct and indirect evidence and found that in patients with AIS, early mechanical thrombectomy with the stent retrievers (Solitaire and Trevo) was associated with higher rates of functional independence compared with Penumbra, and higher rates of successful recanalization than with Merci. Our study also suggested that the 2 stent retrievers (Trevo and Solitaire) performed equally well. These findings tie in with some reported studies.[5,6,11] Our findings regarding sICH and all-cause mortality were inconclusive because of the wide 95% CIs.

The purpose of this NMA was to compare the benefits and risks of the 4 thrombectomy devices for patients with AIS. In line with previous studies,[5,6,11] our result favors the stent retrievers (Solitaire and Trevo) over non–stent retriever devices (Merci and Penumbra) in acute treatment of stroke. Stent retrievers are disposed in the occluded artery and are provisionally expanded into the center of the thrombus. This procedure recanalizes the vessel, affording for reperfusion of the ischemic area and partially entangling the thrombus within the stent.[27] Thrombectomy is implemented by taking back the stents, and this technical evolution was able to extract clots adequately more frequently than could the clot retriever Merci. Theoretically, the advantages of stent retrievers over other devices are that they are more user-friendly, offering a shorter procedural duration, earlier flow restoration, and a higher rate of recanalization.[12,28] Reperfusion after large-vessel occlusion has a strong positive effect on favorable functional outcomes.[29,30] Furthermore, the close relationship between reperfusion and functional outcomes is time dependent,[31] and in this setting, the ability of a stent retriever to achieve faster rates of recanalization and induce a temporary bypass to the tissue before recanalization may perform a vital function.

Some previous studies concluded that the stent devices outperformed the first-generation devices. They found both Solitaire and Trevo achieved significantly higher recanalization rates than

did Merci[5,6,12,32] and greater rates of good functional outcomes,[12,32,33] corroborating our findings. Moreover, in consistent with our results, Dippel et al.[11] also found no evidence for a differential effect of thrombectomy for AIS by stent type.

The most important strength of this study is that for the first time, using rigorous NMA methods, we used direct and indirect evidence to compare and rank the efficacy and safety profiles of thrombectomy devices in patients with AIS, providing the best evaluates of effect. The GRADE approach also permitted reporting of the inerrability in the evidence when accounting for each individual treatment comparison and across the network. The previous meta-analyses were not designed with the view of comparing devices types. Some meta-analyses recruited studies comparing any thrombectomy device with medical treatments of AIS instead of focusing specifically on different devices.[3,4,34-36] Besides, Grech et al.[37] conducted a meta-analysis to compare stent retriever devices versus the first-generation devices or t-PA rather than analyzing each device individually, and thus that study was not powered to analyze the differences in outcome according to device types.

Our results and conclusions are subject to potential limitations. First, because of limited randomized data, we included observational studies, which may introduce heterogeneity. We intended to conduct subgroup analysis according to different design types of studies. However, in the RCT subgroup, 3 arms were deficient so it was not possible to perform NMA. In the observational studies subgroup, the results were in accordance with our main results. Second, our analysis did not correct for important confounders such as the baseline NIHSS of patients and the duration between symptoms onset and arterial puncture. Besides, because of the unavailable individual data of the studies, we were unable to separate patients who were treated with t-PA in devices from those who were not, which may affect the impact of thrombectomy alone and with t-PA on outcomes. Third, the accuracy of our results might be influenced by absent data in unreported trials with negative results and some non-English publications. Fourth, we failed to rank the 2 stent retrievers (Solitaire and Trevo) probably because of the small number of studies included, or maybe these 2 stents performed equally well in reality; more high-quality RCTs are need to evaluate this theory. Moreover, the selection of our outcomes (mRS score at 90 days, TICI score, and incidence of intracerebral hemorrhage within 24 hours with worsening of neurologic status) is appropriate for the purpose of this investigation, whereas others factors might strongly influence outcomes in patients with AIS and have not been included in this systematic review. Despite these limitations, this NMA represents the best available evidence regarding the efficacy and safety of mechanical thrombectomy and is able to assess the positive impact of stent retrievers on clinical outcome in patients with AIS.

CONCLUSIONS

Our study highlights the superiority of stent retrievers (Solitaire and Trevo) over non−stent retriever devices (Merci and Penumbra) in functional outcomes and reperfusion without significant increase in symptomatic hemorrhage or death in patients with AIS. We found no significant difference between the 2 stents. More high-quality RCTs assessing efficacy difference between these 2 stent retrievers are needed.

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REFERENCES

1. Furie KL, Jayaraman MV. 2018 guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2018;49:509-510.
2. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: An updated systematic review and meta-analysis. *Lancet*. 2012;379:2364-2372.
3. Touma L, Filion KB, Sterling LH, Atallah R, Windle SB, Eisenberg MJ. Stent retrievers for the treatment of acute ischemic stroke: a systematic review and meta-analysis of randomized clinical trials. *JAMA Neurol*. 2016;73:275-281.
4. Marmagkiolis K, Hakeem A, Cilingiroglu M, et al. Safety and efficacy of stent retrievers for the management of acute ischemic stroke: comprehensive review and meta-analysis. *JACC Cardiovasc Interv*. 2015;8:1758-1765.
5. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet*. 2012;380:1241-1249.
6. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet*. 2012;380:1231-1240.
7. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39:1205-1212.
8. Friedrich B, Gawlitza M, Fahnert J, et al. Interventional ischemic stroke Treatment—a (r)evolution. *Rofo*. 2016;188:259-267.
9. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019-1030.
10. Hentschel KA, Daou B, Chalouhi N, et al. Comparison of non-stent retriever and stent retriever mechanical thrombectomy devices for the endovascular treatment of acute ischemic stroke. *J Neurosurg*. 2017;126:1123-1130.
11. Dippel DW, Majoie CB, Roos YB, et al. Influence of device choice on the effect of intra-arterial treatment for acute ischemic stroke in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). *Stroke*. 2016;47:2574-2581.
12. Ribo M, Molina CA, Jankowitz B, et al. Stentrievers versus other endovascular treatment methods for acute stroke: comparison of procedural results and their relationship to outcomes. *J Neurointerv Surg*. 2014;6:265-269.
13. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777-784.
14. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*. 2011. Available at: www.handbook.cochrane.org. Accessed March 1, 2018.
15. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105-3124.

16. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res*. 2008;17:279-301.

17. Van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods*. 2016;7:80-93.

18. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3:98-110.

19. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9:e99682.

20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603-605.

21. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009-1018.

22. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. T-PA alone in stroke. *N Engl J Med*. 2015;372:2285-2295.

23. Jovin TG, Chamorro A, Cobo E, et al. REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296-2306.

24. Mendonca N, Flores A, Pagola J, et al. Trevo versus solitaire a head-to-head comparison between two heavy weights of clot retrieval. *J Neuroimaging*. 2014;24:167-170.

25. Leker RR, Eichel R, Gomori JM, de Noriega FR, Ben-Hur T, Cohen JE. Stent-based thrombectomy versus intravenous tissue plasminogen activator in patients with acute middle cerebral artery occlusion. *Stroke*. 2012;43:3389-3391.

26. Jang MU, Hong J, Kang J, et al. Current status of recanalization therapy in acute ischemic stroke with symptomatic intracranial arterial occlusion in korea. *J Stroke Cerebrovasc Dis*. 2014;23:e339-e346.

27. Puñal-Riobóo J, Atienza G, Blanco M. Safety and efficacy of mechanical thrombectomy using stent retrievers in the endovascular treatment of acute ischaemic stroke: a systematic review. *Interv Neurol*. 2015;3:149-164.

28. Kang DH, Park J. Endovascular stroke therapy focused on stent retriever thrombectomy and direct clot aspiration: historical review and modern application. *J Korean Neurosurg Soc*. 2017;60:335-347.

29. Zangerle A, Kiechl S, Spiegel M, et al. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. *Neurology*. 2007;68:39-44.

30. Mazighi M, Serfaty JM, Labreuche J, et al. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. *Lancet Neurol*. 2009;8:802-809.

31. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology*. 2009;73:1066-1072.

32. Broussalis E, Trinka E, Hitzl W, Wallner A, Chroust V, Killer-Oberpfalzer M. Comparison of stent-retriever devices versus the Merci retriever for endovascular treatment of acute stroke. *AJNR Am J Neuroradiol*. 2013;34:366-372.

33. Deshaies EM, Singla A, Villwock MR, Padalino DJ, Sharma S, Swarnkar A. Early experience with stent retrievers and comparison with previous-generation mechanical thrombectomy devices for acute ischemic stroke. *J Neurosurg*. 2014;121:12-17.

34. Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke. *JAMA*. 2015;314:1832.

35. Bush CK, Kurimella D, Cross LJS, et al. Endovascular treatment with stent-retriever devices for acute ischemic stroke: a meta-analysis of randomized controlled trials. *PLoS One*. 2016;11:e147287.

36. Elgendy IY, Kumbhani DJ, Mahmoud A, Bhatt DL, Bavry AA. Mechanical thrombectomy for acute ischemic stroke: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2015;66:2498-2505.

37. Grech R, Pullicino R, Thornton J, Downer J. An efficacy and safety comparison between different stentriever designs in acute ischaemic stroke: a systematic review and meta-analysis. *Clin Radiol*. 2016;71:48-57.

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