Neurology Asia 2020; 25(4) : 439 – 446

ORIGINAL ARTICLES

Efficacy and safety of endovascular treatment vs medical treatment in anterior circulation stroke beyond 6 Hours: A systematic review and meta-analysis

*[1,2]Zixu Zhao *MD*, *[1,3]Xin Jiang *MD*, [3]Ying Zhang *MD*, [4]Zixiao Yin *MD*, [1]Guohui Lu *MD*, [1]Yang Wang *MD*, [5]Michael Hall *PhD*, [1]Lingfeng Lai *MD*

*ZX Zhao and X Jiang contribute equally to this work and are co-first author

[1]Department of Neurosurgery, the First Affiliated Hospital of Nanchang University, Nanchang; [2]Queen Mary School, Jiangxi Medical College, Nanchang University, Nanchang; [3]The First Clinical Medical School, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi; [4]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [5]Institute of Ophthalmology, University College London, London, UK

Abstract

Background & Objective: Endovascular treatment is the widely accepted treatment for patients with anterior circulation stroke within 6 hours of onset of stroke. We aimed to evaluate the advantages of endovascular treatment compared to standard medical treatment in treating patients with anterior circulation stroke beyond the 6-hour therapeutic window. *Methods:* We reviewed the literature concerning endovascular treatment versus medical treatment beyond the 6-hour therapeutic window. Using random-effects meta-analysis, we evaluated the following outcomes: modified Rankin scale in the three-month follow-up [excellent outcome (mRS≤1), functional independence (mRS≤2), moderate outcome(mRS≤3)], recanalization rate at 24 hours, mortality at 90 days or in-hospital, symptomatic intracranial hemorrhage, parenchymal hematoma type 2 and hemorrhagic infarction 1. *Results:* Four studies including 642 patients were evaluated. Endovascular treatment was associated with higher odds of excellent outcome (OR 2.55; 95% CI 1.48 to 4.41,), functional independence (OR 3.64; 95% CI 2.43 to 5.45), moderate outcome (OR 2.70; 95% CI 1.95-3.74) and recanalization rate at 24 hours (OR 8.81; 95%CI 2.81 to 27.69) compared to MT. No difference in the rates of mortality, symptomatic intracranial hemorrhage, parenchymal hematoma type 2 or hemorrhagic infarction 1 was found between the 2 groups. Studies using strict perfusion imaging inclusion selection showed better moderate outcome in comparison to the studies without perfusion imaging inclusion selection (P <0.012).
Conclusion: Our study highlights the superiority of endovascular treatment over standard medical treatment alone for treating patients with anterior circulation stroke beyond 6 hours since stroke onset, although more studies are required for further investigation. Standard of strict selection for eligible patients before endovascular treatment should be based on DAWN or DEFFUSE 3 inclusion criteria.

Keywords: Endovascular procedure, cerebral artery, stroke, perfusion imaging

INTRODUCTION

For patients with anterior circulation stroke (ACS) whose onset of symptom are within 6 hours, endovascular treatment (EVT) is currently recommended based on the evidence provided by previous randomized control trials (RCTs).[1-5] However, patients presenting to hospital beyond 6 hours since stroke onset or the last time seen well accounted for up to 23% of the total patients with acute ischemic stroke.[6] Given that a large proportion of patients exceeds the generally accepted therapeutic window (6 hours) for endovascular treatment, confirmation of the

Address correspondence to: Lingfeng Lai. Department of Neurosurgery, The First Affiliated Hospital of Nanchang University, 17 Yong Wai Zheng Street, East Lake District, 330006, Nanchang, Jiangxi, China. Tel: +86 18870052335, E-mail: laiweiwei1986@163.com

Date of Submission: 24 April 2020; Date of Acceptance: 30 June 2020

optimal treatment either by EVT or standard medical treatment (MT) is required to be established. In addition, uncertainties still exist in the inclusion criteria of EVT for eligible patients beyond 6 hours since stroke onset.

Currently, the published literature on this subject is limited and often compromised in the context of our study. One study included two subgroup studies of two RCTs containing patients who were treated beyond 5.5 hours and 4.5 hours respectively, which were still considered within 6 hours therapeutic window.[7] Another two studies were two-arm studies which primarily compared outcomes of patients treated within 6 hours with those beyond 6 hours by EVT which has been suggested to be less clinically applicable.[8,9]

As more on-going RCTs are committed to investigate on the feasibility of EVT for patients with ischemic stroke[10], the purpose of this study is to evaluate the potential advantages of EVT comparing to MT in treating patients with ACS beyond 6 hours since stroke onset, as well as to provide statistical evidence for the standard of selecting eligible patients for EVT.

METHODS

Literature search

Literatures were systematically searched by two reviewers on PubMed, EMBASE and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register) from inception to June 3, 2019. For the search strategy, we combined the terms (stroke OR brain infarction OR cerebrovascular disorder) and (endovascular treatment OR thrombectomies) with (time OR onset). Reference lists and cited articles were also cross-checked for potentially eligible publications. The study was conducted corresponding to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRIMA) guidelines and was registered at PROSPERO, number CRD42019138339.

Quality assessment

Two reviewers independently assessed the risk of bias. The publication bias of RCTs was evaluated by Cochrane risk of bias assessment by assessing the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias.[11] Whereas the quality of cohort studies was assessed by using the Newcastle-Ottawa Scale, including selection, comparability and outcomes.[12]

Selection criteria

All studies were checked by title and abstract following the inclusion criteria. Included were: (1) patients with ACS treated ≥6 hours since stroke onset (2) Studies comparing EVT to MT separately. Exclusion criteria were: (1) trials included fewer than 10 participants (2) Endovascular devices used were no longer able to find in the market (3) Patients with posterior circulation stroke or with ACS treated within 6 hours after the onset of symptoms. There was no language barrier during selection. RCTs, cohort studies, as well as matched case control studies were all included.

Outcome variables

Efficacy outcomes were defined by the Modified Rankin scale (mRS), measured 90 days after intervention. An excellent outcome scored mRS≤1, functional independence as mRS≤2, and moderate outcome as mRS≤3.[13,14] Safety outcomes considered the following: Recanalization rate; all-cause mortality after 90 days or hospitalized, symptomatic intracranial hemorrhage (sICH), Parenchymal hematoma type 2 (PH2), and hemorrhagic infarction 1 (HI1).[15]

Data extraction

Data extraction was conducted by two reviewers independently. Study titles, abstracts, and studies that satisfied the inclusion criteria were retrieved for further screening. The full text of eligible studies was extensively reviewed in accordance with the criteria of inclusion and exclusion outlined above. Any disagreements were arbitrated by a third reviewer. The main extracted data considered study setting, sample size, baseline of stroke patient characteristics (age, sex, risk factors and initial imaging findings), thrombectomy devices, efficacy and safety outcomes, and information for assessment of the risk of bias.

Statistics analysis

Characteristics of patients were presented as numbers and percentages for categorical variables, and continuous data were expressed as means ± standard deviation (SD). The differences of baseline in between EVT and MT were evaluated by Chi2-test for dichotomous variable and T-test for continuous variable. Odds ratio (OR) with 95% confidence intervals were calculated and

pooled for each outcome of interest. Due to the assumptions of clinical diversity and differences in methodology among the included studies, the random effects model was implemented. The statistical heterogeneity between studies were assessed using the Q test and the calculation of I^2. We considered substantial heterogeneity if $p < 0.10$ or $I^2 \geq 50\%$. When significant heterogeneity existed, subgroup analysis was conducted to analyse the source of heterogeneity. [16] Comprehensive Meta-Analysis (CMA) 2.0 (Biostat, Englewood, NJ) was used to perform the data analysis.

RESULT

Study selection and characteristics

A total of 1686 articles were found in the initial identification of literatures, of which 1617 were excluded based on the title of the study. Of the remaining 69 papers, 42 were excluded, which were evaluated carefully by two independent reviewers. Ultimately, 4 studies were selected. 12 were excluded due to lack of comparison group, 8 were excluded because of non-appropriate therapeutic window, 2 were excluded for repetition, and 1 was excluded considering its unavailable result. (Figure 1)

In total, 4 articles with 642 patients were included in this study.[17-20] Two studies—DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) and Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (DEFUSE 3) were randomized multicenter studies with strict selection criteria for eligible patients. One study was a post hoc study collecting data from 5 RCTs. Another was a matched case control study which had higher risk of bias. Patient characteristics were listed in the Table 1: numbers of patients, study design, device of EVT, age, gender, underlying diseases, and NIHSS scores on admission were evaluated.

One hundred and fifty patients from the Post hoc study was excluded during baseline analysis, and 492 patients from the remaining 3 studies were included. The median age of the patients was 69.0 in EVT and 69.7 in MT. The proportion of male in EVT was 45.4%, which was significantly lower than that in MT group (P<0.02). 78.5% in EVT and 74.3% in MT showed hypertension. In EVT, 25.9% of patients had diabetes in comparison to 28.6% in MT. The NIHSS score of patients did not differ significantly between EVT and MT, at 16.32 and 15.93 respectively (Table 2).

Outcomes

Efficacy outcome: EVT was associated with

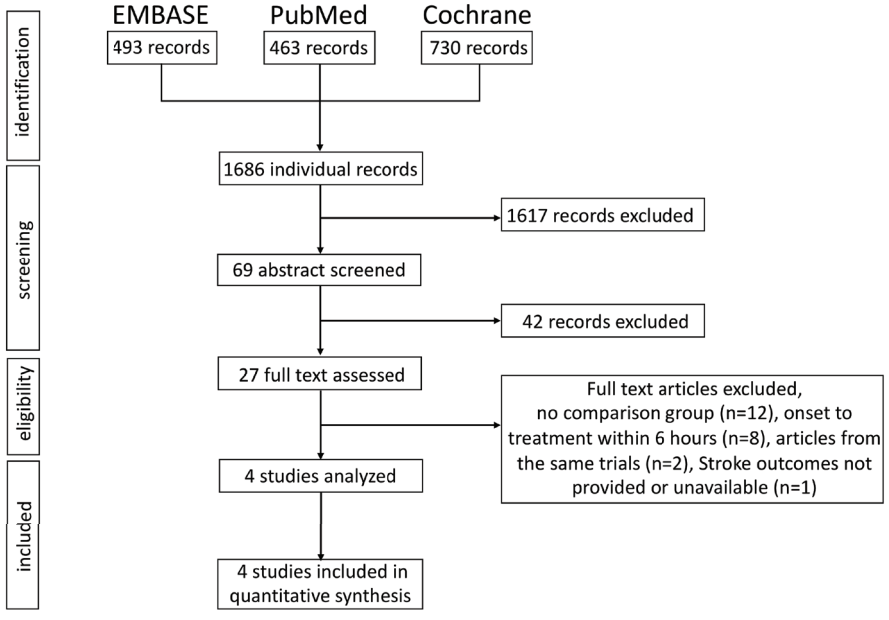

Figure 1. PRISMA flow chart of the included studies.

higher odds of excellent outcome (Odds Ratio, 2.55; 95% confidence interval [CI], 1.48-4.41; I^2, 27.6%), functional independence (OR, 3.64; CI, 2.43-5.45; I^2, 65.4%) and moderate outcome (OR, 2.71; 95% CI, 1.65-4.43; I^2, 55.0%) comparing to MT. (Figure 2)

Safety outcome: EVT was associated with significantly higher odds of recanalization rate at 24 hours (OR, 7.81; CI, 4.85-12.59, I^2, 27.6%). There was no statistically significant difference in mortality (OR, 0.82; 95% CI, 0.50-1.33; I^2, 16.7%), sICH (OR, 1.327; 95% [CI], 0.59-3.00; I^2, 15.07%), HI1 (OR, 1.57; 95% [CI], 0.71-3.46; I^2, 0.80%) and PH2 (OR, 2.13; 95% [CI], 0.54-8.42; I^2, 0.00%). (Figure 3)

Subgroup study: We performed a subgroup analysis to determine whether moderate outcome differed between two subgroups, categorized by whether DAWN or DEFFUSE 3 criteria of Perfusion Imaging Inclusion Selection (PIIS) was used, in order to include eligible patients undergoing EVT. In the subgroup without PIIS, EVT was associated with better moderate outcome comparing to MT (OR, 1.72; CI, 1.03-2.86; I^2, 1.03-2.86), which was as same as the result in the subgroup with PIIS (OR, 3.68; CI, 2.41-5.62; I^2, 1.03-2.86). Statistical significance of Odds ratio between the two subgroups was observed by using z-test, as the subgroup with PIIS showed better moderate outcome ($p<0.012$).

Quality assessment

Risk of bias was evaluated as low for RCTs, based on assessment by the Cochrane Collaboration's tool (Table 3). In regard to the matched case control study, Newcastle-Ottawa scale quality score was 7 stars, representing good quality.

DISSCUSION

Our meta-analysis showed that patients with ACS beyond 6 hours since stroke onset who were treated with EVT had higher rates of excellent outcome, function independence outcome, moderate outcome and recanalization rate at 24 hours, relative to MT patients. However, no statistical difference in mortality or post-operational complications (sICH, PH2, HI1) was observed.

EVT can improve functional independence more significantly than MT, which is in line with the results from a previous study.[21] Several mechanisms have been implicated that could explain the benefits of EVT over medical treatment in treating patients beyond 6 hours.

Table 1: Study characteristics

Author, Journal	NO. of EVT/MT Patients	Study Design	Device of EVT	Mean Age of EVT/MT	%Male EVT/%MT	Hypertension of EVT/MT Patients	Diabetes of EVT/MT patients	History of stroke of EVT/ MT patents	Mean NIHSS score of EVT/ MT patients
Qureshi *et al.*[17]	52/52	MCCS	SR, NOA	66.4/65.4	69.0/69.7	78.5/74.3	25.9/28.6	12.4/13.7	16.3/15.9
Saver *et al.*[18]	80/70	PHS	SR, NOA	64.5/NA	46.8/NA	58.2/NA	13.9/NA	8.9/NA	16.1/NA
Nogueira *et al.*[19]	107/99	RCT	SR, CA	69.4/70.7	69.4/70.7	77.6/75.7	24.2/31.3	11.2/11.1	5.9/5.2
Albers *et al.*[19]	92/90	RCT	SR	70/0/71.0	70.0/71.0	77.2/80.0	30.4/30.0	14.1/13.3	7.4/6.7

AD indicates aspiration device; NIHSS, national institutes of health stroke scale; MCCS, matched case control study; PHS, post hoc study; RCT: randomized control trail; EVT, endovascular treatment; SR, stent retriever; NOS, not otherwise specified, NA, not available.

Table 2: Pooled value of patient characteristics

	EVT	MT	p value
Age	69.00(14.82)	69.67(13.89)	NS
Male	45.42%	56.02%	<0.02
Hypertension	78.50%	74.30%	NS
Diabetes	25.90%	28.60%	NS
History of stroke	12.40%	13.70%	NS
NIHSS score	16.32(5.83)	15.93(6.07)	NS

EVT, endovascular treatment; MT, medical treatment; NS, not significance
The data are represented either by "mean ± standard error" or by percentage.
We did not include 150 patients of the Post hoc study since baseline of the trial was absent

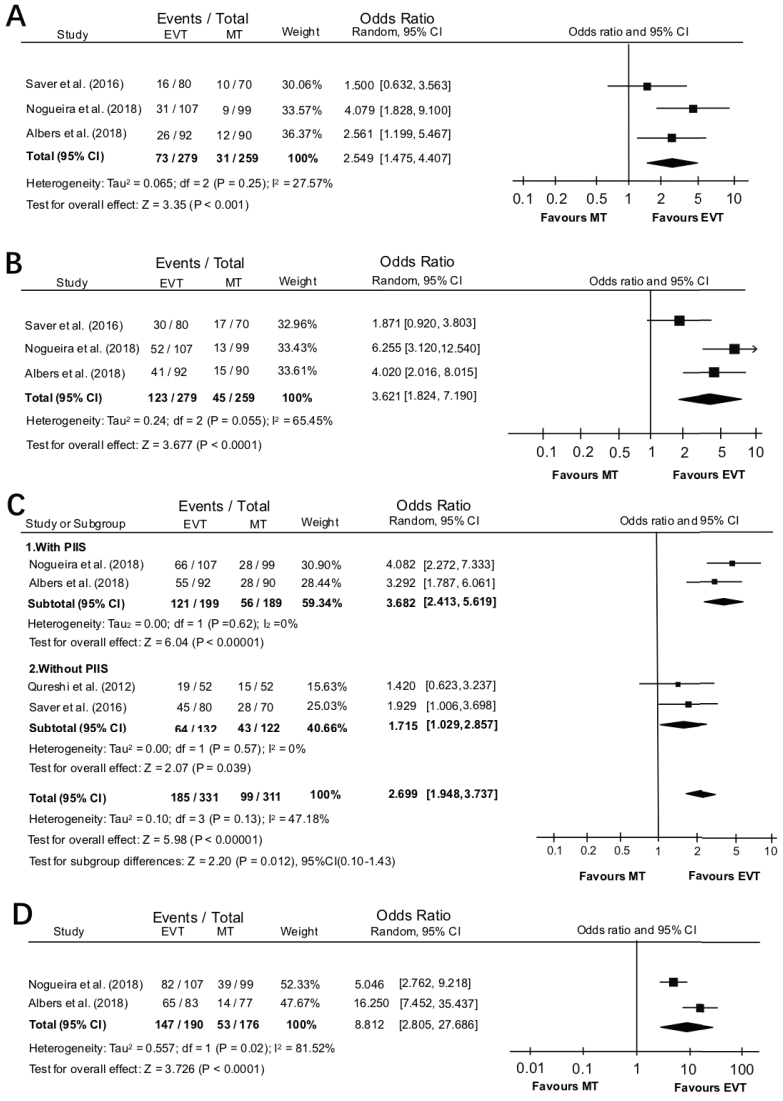

Figure 2. Pooled analysis of efficacy outcome of all included studies reporting patients receiving endovascular treatment and patients receiving medical treatment. A. Excellent outcome (mRS≤1); B. functional independence (mRS≤2); C. moderate outcome (mRS≤3). Definitions of outcomes based on mRS score in the three-months follow-up; D. recanalization rate at 24 hours. EVT indicates endovascular treatment; MT, medical treatment; PIIS, perfusion imaging inclusion selection.

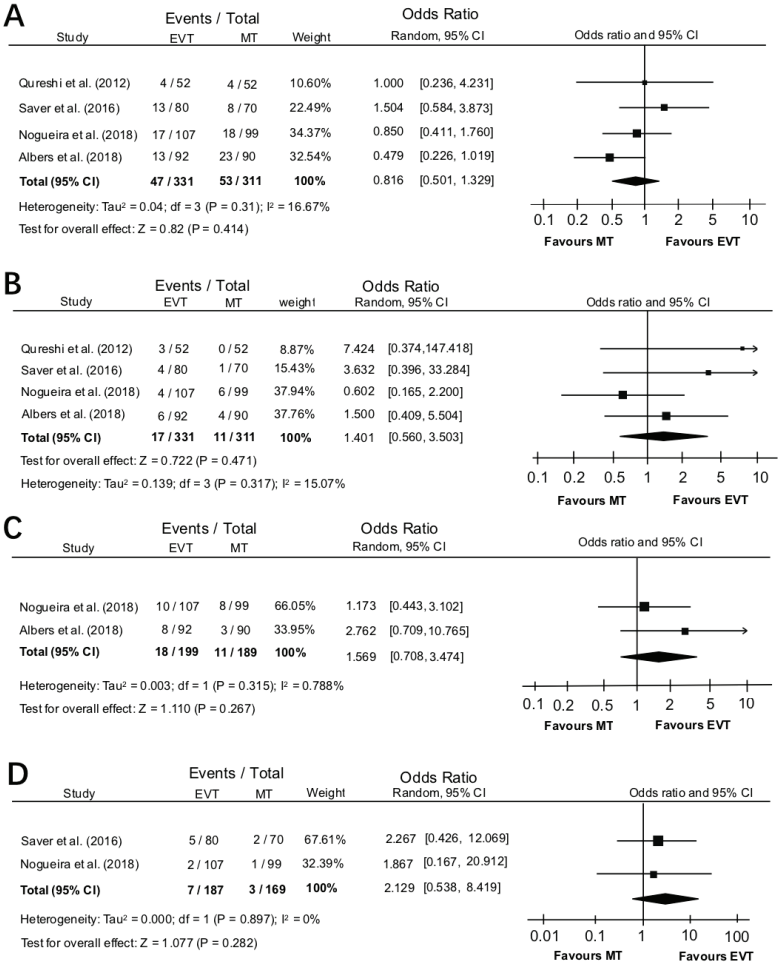

Figure 3. Pooled analysis of safety outcome of all included studies reporting patients receiving endovascular treatment and patients receiving medical treatment. A. all-cause mortality at 90 days or at in-hospital; B. symptomatic intracranial haemorrhage (sICH); C. hemorrhagic infarction 1 (HI1); D. Parenchymal hematoma type 2 (PH2). EVT indicates endovascular treatment; MT, medical treatment.

Table 3: Assessment of the risks of different bias for RCTs by using Cochrane risk of bias tool

	DAWN 2018	DEFFUSE 3 2018	ESCAPE 2018	REVASCAT 2015	MR CLEAN 2015	SWIFT PRIME 2015	EXTEND-IA 2015
Random sequence generation (selection bias)	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+	+	+	+	+

The eligibility for PIIS among patients is commonly discussed. With the help of mismatch-evaluating software, patients in DAWN and DEFFUSE 3, whose volumes of ischemic core and perfusion lesion were able to be calculated, had better outcomes treated by EVT comparing to MT.[19,20] In the post hoc study, Simone *et al* reported that selecting patients by using perfusion imaging could optimize EVT to treat patients within 6 hours.[7] However, insufficient evidence was provided in that article. In our study, after comparing studies that used PIIS with those did not, we found that EVT was associated with better moderate outcome in those trials with PIIS ($p<0.012$).

Pre-operative factors might also attribute to the better clinical outcomes seen among patients treated by EVT. Intravenous (IV) alteplase, an effective thrombolytic agent, is recommended for acute ischemic stroke within 4.5 hours since onset of symptoms.[22] 8.7% of patients in DAWN were administrated with intravenous alteplase (IV-tPA)[19], and fewer than 10% in the DEFFUSE 3 group.[20] In contrast, the overall rate of patients in the post hoc analysis who were administrated with IV-tPA) was 45.6% in MT.[18] Different IV-tPA rates likely explain the differences of functional independence between trials, as the percentage of functional independence among patients treated by MT in the post hoc analysis was 24.3%, whereas that in a pooled study of DAWN and DEFFUSE 3 was 15%.[18,21] Lower IV-tPA rate in DAWN is likely attributed to the fact that the majority of patients in this trial were not administrated with IV-tPA, as they exceeded the 4.5 hour therapeutic window for IV-tPA treatment.[23] However, as the therapeutic window of IV-tPA extended to 9 hours, especially when thrombolysis showed a significantly better outcome than placebo in treating mismatch patients beyond 4.5 hours, more clinical trials should be conducted aiming at evaluating potential advantages and disadvantages of EVT in comparison to thrombolysis beyond 6 hours.[24]

In addition, Davison *et al*. suggested that male patients with acute ischemic stroke treated with thrombectomy were more likely to be associated with better outcomes due to larger cerebral arterial diameters than female patients.[25] In our study, there were more male patients in MT than in EVT, although the outcome in EVT was more favorable than MT, suggesting that EVT success is independent of gender.

Recanalization rates after EVT are considered an indicator of improved patient outcome[18], as reflected by improved functional outcomes and reduced mortality.[26] Siomone *et al*. reported higher odds of recanalization rate in EVT in comparison to MT among patients with ACS beyond 6 hours.[7] In our study, we also found a significant advantage of EVT in improving recanalization rate, implying a better treatment outcome comparing with MT.

We did not find significant difference in mortality and post-operative complications (sICH, PH2, HI1) between EVT and MT, which is consistent with the results from previous analyses.[7] However, this did not negate the benefit of EVT in treating ACS as it can significantly improve neurological recovery and favorable outcomes in comparison to MT, which was also observed among patients within 6 hours since stroke onset.[27]

The limitations of this study should be noted. Firstly, due to lack of data in the Post hoc study, we were not able to investigate heterogeneity, including subgroup study and test for sensitivity. We did, however, attempt to reduce statistics bias by applying the random-effect model. Secondly, one of the included studies was published before the "pre-stentriever era", which is not considered in current guidance. Despite this, intra-arterial and clot retrieval devices are still utilized in the present real-world practice. Lastly, our included studies were limited by various flaws in study design, including enrollment criteria and baseline information, which could be subject to unconscious bias.

In conclusion, although more studies are required for further investigation, our study highlights the superiority of endovascular treatment over standard medical treatment alone for treating patients with anterior circulation stroke beyond 6 hours since stroke onset. We propose that the standard for selection of eligible patients before EVT should be based on DAWN or DEFFUSE 3 inclusion criteria.

DISCLOSURE

Financial support: This work was supported by The Department of Education of Jiangxi Province grant number 180001.

Conflict of interest: None

REFERENCES

1. Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Eng J Med* 2015;372(11):1019-30.
2. Saver JL, Goyal M, Bonafe A, *et al*. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone

in stroke. *N Eng J Med* 2015;372(24):2285-95.
3. Campbell BCV, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Eng J Med* 2015;372(11):1009-18.
4. Jovin TG, Chamorro A, Cobo E, *et al*. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Eng J Med* 2015;372(24):2296-306.
5. Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Eng J Med* 2015;372(1):11-20.
6. Tong D, Reeves MJ, Hernandez AF, *et al*. Times from symptom onset to hospital arrival in the get with the guidelines-stroke program 2002 to 2009: Temporal trends and implications. *Stroke* 2012;43(7):1912-7.
7. Vidale S, Longoni M, Valvassori L, Agostoni E. Mechanical Thrombectomy in strokes with large-vessel occlusion beyond 6 hours. *J Clin Neurol* 2018;14(3):407-12.
8. Wareham J, Phan K, Renowden S, Mortimer AM. A Meta-analysis of observational evidence for the use of endovascular thrombectomy in proximal occlusive stroke beyond 6 hours in patients with limited core infarct. *Neurointervention* 2017;12(2):59-68.
9. Li X, Wu L, Xie H, Bao Y, He D, Luo X. Endovascular treatment for ischemic stroke beyond the time window: a meta-analysis. *Acta Neurol Scand* 2020;141(1):3-13.
10. Sarraj A. SELECT 2: A randomized controlled trial to optimize patient's selection for endovascular treatment in acute ischemic stroke. C*linicaltrials* https://clinicaltrials.gov/ct2/show/NCT03876457?term=NCT03876457&rank=1. Accessed October 5, 2019.
11. Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Online)* 2011;343(7829):1-9.
12. 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(9):603-5.
13. Bamford JM, Sanderock PAG, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;20(6):828.
14. Wilson JTL, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: Benefits of a structured interview. *Stroke* 2005;36(4):777-81.
15. Berger C, Fiorelli M, Steiner T, *et al*. Hemorrhagic transformation of ischemic brain tissue asymptomatic or symptomatic? *Stroke* 2001;32(6):1330-5.
16. Altman DG, Bland JM. Interaction revisited: The difference between two estimates. *BMJ* 2003;326(7382):219.
17. Qureshi AI, Miley JT, Chaudhry SA, *et al*. Safety and effectiveness of endovascular treatment after 6 hours of symptom onset in patients with anterior circulation ischemic stroke : A matched case control study. *J Stroke Cerebrov Dis* 2013;22(7):1076-81.
18. Saver JL, Goyal M, Van Der Lugt A, *et al*. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: Ameta-analysis. *JAMA* 2016;316(12):1279-88.
19. Pereira VM, Mehta BP, Baxter BW, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Eng J Med* 2018;378:11-21.
20. Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Eng J Med* 2018;378(8):708-18.
21. Snelling B, Mccarth DJ, Chen S, *et al*. Extended window for stroke thrombectomy. *J Neurosci Rural Pract* 2019;10(2):294-300.
22. Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019;50:e314-e418.
23. Emberson J, Lees KR, Lyden P, *et al*. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384(9958):1929-35.
24. Campbell BCV, Ma H, Ringleb PA, *et al*. Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet* 2019;394(10193):139-47.
25. Davison MA, Ouyang B, Keppetipola KM, Chen M. Arterial diameter and the gender disparity in stroke thrombectomy outcomes. *J NeuroInterv Surg* 2018;10(10):949-52.
26. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: A meta-analysis. *Stroke* 2007;38(3):967-73.
27. Goyal M, Menon BK, Van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387(10029):1723-31.