



# Endovascular treatment or general treatment: how should acute ischemic stroke patients choose to benefit from them the most?

## A systematic review and meta-analysis

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### Abstract

**Background:** Acute ischemic stroke due to large-vessel occlusion is a leading cause of death and disability, and therapeutic time window was limited to 4.5 hour when treated with intravenous thrombolysis. It has been acknowledged that endovascular treatment (EVT) is superior to general treatment (only medication, including intravenous recombinant tissue plasminogen activator (rt-PA)) in improving the outcome of AIS since 2015. However, the benefits were limited to improvement of functional outcomes and functional independence. Hence, this meta-analysis was conducted to summarize the benefits of EVT for acute ischemic stroke, explore underlying indications of EVT for AIS patients and suggest implications for clinical practice and future research.

**Methods:** A search was performed to identify eligible studies in PubMed, Scopus and Web of Science updated to February 5, 2019. Functional outcomes, the modified Rankin Scale (mRS) 0–1, mRS 0–2, all-cause mortality, symptomatic intracerebral hemorrhage and asymptomatic intracerebral hemorrhage (aICH) at 90 days were selected as outcomes. Data was pooled to calculate the odds ratio (OR) and 95% confidence interval (CI). Heterogeneity, subgroup analysis, sensitivity analysis and publication bias were also performed in this meta-analysis.

**Results:** Eighteen studies comprising 3831 patients were included and analyzed in this meta-analysis. In comparison with general treatment, improved functional outcomes (mRS 0–1: OR=1.68, 95% CI=1.43–1.97, inconsistency index [ $I^2$ ]=57%,  $P < .00001$ ; mRS 0–2: OR=1.78, 95% CI=1.55–2.03,  $I^2=69%$ ,  $P < .00001$ ), reduced risk of all-cause mortality (OR=0.82, 95% CI=0.70–0.98,  $I^2=27%$ ,  $P=.03$ ) but higher risk of aICH (OR=1.43, 95% CI=1.05–1.95,  $I^2=0%$ ,  $P=.02$ ) at 90 days were found in AIS patients treated with EVT. Age < 70, National Institutes of Health Stroke Scale  $\geq 20$  and maximum delay for invention > 5 hours could improve clinical outcomes following EVT. In sensitivity analysis, it showed that 2 studies had a great influence on the pooled ORs. No potential publication bias was found in this meta-analysis.

**Conclusion:** Taken together, EVT, which led to improved functional outcomes and decreased risk of death, is superior to general treatment for AIS patients with age < 70, National Institutes of Health Stroke Scale  $\geq 20$  and maximum delay for invention > 5 hours. Moreover, it suggests that “with mechanical thrombectomy” is potential favorable factor for improving aICH in comparison with general treatment.

**Abbreviations:** aICH = asymptomatic intracerebral hemorrhage, AIS = acute ischemic stroke, CI = confidence interval, EVT = endovascular treatment,  $I^2$  = inconsistency index, IA = intra-arterial, IV t-PA = intravenous tissue plasminogen activator, LVO = large vessel occlusions, Max = maximum, MeSH = medical subject headings, mRS = modified ranking scale, MT = mechanical

Editor: Weimin Guo.

This work jointly supported by grants from the National Natural Science Foundation of China (No.81774230, 81571003), Science and Technology Project of Wenling City (No.2017C311117) and Basic Public Welfare Research Project of Zhejiang Province (No.LGN18A010001).

All data analyzed during this study are included in this article.

Ethics approval and consent to participate was not applicable.

Consent for publication was not applicable.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Yang W, Zhang L, Yao Q, Chen W, Yang W, Zhang S, He L, Li H, Zhang Y. Endovascular treatment or general treatment: how should acute ischemic stroke patients choose to benefit from them the most? A systematic review and meta-analysis. *Medicine* 2020;99:20(e20187).

Received: 31 October 2019 / Received in final form: 12 March 2020 / Accepted: 6 April 2020

<http://dx.doi.org/10.1097/MD.00000000000020187>

thrombectomy, NIHSS = National Institutes of Health Stroke Scale, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, RCT = randomized controlled trials, sICH = symptomatic intracerebral hemorrhage, vs = versus.

**Keywords:** endovascular treatment, intracranial hemorrhages, IV t-PA, stroke

## 1. Introduction

Stroke is a leading cause of death and disability worldwide, especially in the current aging society.<sup>[1]</sup> Thrombolytic therapy with intravenous tissue plasminogen activator (IV t-PA) has saved massive acute ischemic stroke (AIS) patients by promoting thrombolysis and reopening of the occluded blood vessels. Therefore, IV t-PA has been recommended as the standard medical treatment and it is the only drug approved by the Federal Drug Administration for AIS.<sup>[2,3]</sup> Unfortunately, IV t-PA has a circumscribed thrombolytic window. It means that IV t-PA has clinical effect only in the first 3.0 to 4.5 hours after the onset of stroke, after which the possibility of neurological and functional recovery decreases dramatically.<sup>[4,5]</sup> Taken together, the short therapeutic window and the extensive set of clinical eligibility criteria for administration limit the application of IV t-PA.

In view of the narrow time limit of IV t-PA, endovascular treatment (EVT) focusing on relieving vessel occlusion in stroke has been developed as an alternative for IV t-PA or as an adjunct in the management over the past few years.<sup>[6,7]</sup> EVT, including intra-arterial (IA) thrombolysis, intravascular stent, and mechanical thrombectomy (MT), has shown significant superiority in the recanalization rate. However, the disadvantage of the long time for administration hinders the development of EVT. As a consequence, the clinical superiority of EVT is skeptical. In paralleled with IV t-PA, EVT has been associated with a higher likelihood of recanalization; however, evidence from nine trials has shown no significant superiority of EVT compared with general treatment (only medication, including intravenous recombinant tissue plasminogen activator (rt-PA)) before 2015.<sup>[8–15]</sup> In contrast, accumulating evidence has demonstrated that EVT with improved devices and techniques offers significant benefits compared with general treatment after 2015.<sup>[16–25]</sup> However, the justification of benefits were limited to improvement of functional outcomes and functional independence.

Overall, this meta-analysis was devoted to summarize the benefits of EVT for AIS, explore underlying indications of EVT for AIS patients, and suggest implications for clinical practice and future research.

## 2. Methods

### 2.1. Study protocol

This meta-analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses statement (Additional file 1).<sup>[26]</sup>

### 2.2. Eligibility criteria

Studies were included if they were prospective randomized controlled trials (RCTs) published in English that fulfilled the following criteria:

(1) Studies compared EVT (intervention group) with general treatment (control group) including intravenous t-PA and heparin in AIS.

- (2) All studies were limited to those involving human subjects.
- (3) If duplicate studies with an accumulating number of patients or something else were published, only the most complete studies were included in the analysis performed in this study.
- (4) Study populations were not less than 25 patients.
- (5) Study with only IA thrombolysis in EVT group was excluded.
- (6) Patients suffered from stroke due to major vessel occlusion, which was confirmed by imaging examination, and had received treatment with EVT or general treatment or both.
- (7) Studies reported the following outcomes: all-cause mortality or functional outcome measured by modified Rankin Scale (mRS) or symptomatic intracerebral hemorrhage (sICH) or asymptomatic intracerebral hemorrhage (aICH).
- (8) There were no restrictions on the information of EVT and general treatment, year of the study, patient age, imaging criteria, and National Institutes of Health Stroke Scale (NIHSS) score.

### 2.3. Literature search strategy

PubMed, Scopus and Web of Science were searched for studies published or presented on or before February 5, 2019. All publications are in English. To achieve maximum sensitivity of the search strategy and to include more extensive studies, Medical Subject Headings (MeSH) terms and the keywords that were retrieved in the field of Title/Abstract were used in combination. The search strategy consisted of three parts. “Endovascular” was selected in the MeSH term and “Endovascular treatment”, “Endovascular procedures”, “Endovascular therapy”, “Intra-arterial”, “Thrombectomy”, “Thrombolysis” were retrieved in the field of Title/Abstract. All the above were connected by “OR”. “Stroke” was selected in the MeSH term. Then, “Randomized controlled trial” was selected in the MeSH term. Ultimately, “AND” was used to connect the three parts. All relevant articles were retrieved first, and then irrelevant articles were manually excluded through title and abstract screening and full-text assessment. In addition, special attention was paid to the references of included studies to identify more candidate studies. All work was conducted independently by two investigators to avoid selection bias.

### 2.4. Data extraction and quality assessment

All data were extracted independently from the tables and figures of included studies by two investigators in an unblinded fashion. Moreover, another investigator took responsibility for the accuracy and reliability of all of the extracted data. NIHSS, serving as a predictive tool of the functionality of the AIS patient, is the most widespread clinical scale.<sup>[27]</sup> Therefore, the study characteristics (author, publication year, study period, country, number of medical centers, and study design), main characteristics of the patients (age, gender, and NIHSS), information on the intervention, outcome measure, maximum delay in the intervention and outcome of the intervention (mRS, intracerebral hemorrhage, and all-cause mortality), and control groups were extracted independently by two authors. The quality of the included studies was assessed by two other authors using the Cochrane Risk of Bias tool.<sup>[28]</sup>

## 2.5. Outcome measure

The mRS is an evaluation tool to assess the clinical poststroke functional independence (detailed grades of mRS: 0 - No symptoms; 1 - No significant disability; 2 - Slight disability; 3 - Moderate disability; 4 - Moderately severe disability; 5 - Severe disability; 6 - Dead)<sup>[29,30]</sup>. The prespecified primary outcome measures were the mRS score of 0–1 and the mRS score 0–2 at 90 days. In addition, a 90-day mRS score of 0–1 and a 90-day mRS score of 0–2 were defined as an excellent outcome and a good outcome, respectively. The prespecified secondary outcome measures were intracerebral hemorrhage and all-cause mortality at 90 days.

## 2.6. Statistical analysis

Statistical analysis was conducted using Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (Stata Corp LP, College Station, TX, USA). The combined effect of odds ratio (OR) and 95% confidence interval (CI) were defined by a random-effect model or a fixed-effect model. The heterogeneity among included studies was tested using the inconsistency index ( $I^2$ ). A random effect model was used when there was a high level of heterogeneity. Publication bias was evaluated qualitatively by visual observation of funnel graphs and was assessed quantitatively by the Begg's rank correlation method (Stata 12.0), which indicated a publication bias with  $P < 0.05$ . A  $P$  value of  $< 0.05$  was considered statistically significant. For indicators with high heterogeneity, sensitivity analysis was carried out with the Stata 12.0 software to identify the origin of heterogeneity and reliability of the meta-analysis. In addition, included studies were excluded one by one to perform sensitivity analysis. Subgroup analysis were utilized to uncover the effect of maximum (max) delay for intervention, stroke severity, age and MT on EVT.

## 3. Results

### 3.1. Eligible studies and study characteristics

Detailed steps of the inclusion and exclusion criteria of the study are shown in Fig. 1. Briefly, a total of 6301 studies were retrieved through four electronic database searches. Twenty-one additional studies were identified from the references of included studies after removing the duplicates. After the layer-by-layer screening, the final meta-analysis was performed after complete evaluation of 18 studies that met the inclusion criteria.<sup>[8–25]</sup> The basic characteristics of the included studies and patients are summarized and shown in Tables 1 and 2, respectively. A total of 3831 patients were enrolled in the 18 included studies. The included studies were evaluated objectively and the quality of included studies was proved to be generally high (Table 3).

### 3.2. Primary outcome

The excellent outcome, mRS 0–1 at 90 days, was observed after EVT (Fig. 2A). A significant difference was found in mRS 0–1 after 90 days between EVT and general treatment (OR=1.68, 95% CI=1.43–1.97,  $I^2=57%$ ,  $P < .00001$ ). Another primary outcome measure, mRS 0–2 at 90 days, was favored in the intervention group (Fig. 2B). In comparison with the control group, the intervention group showed a statistically significant difference in mRS 0–2 at 90 days (OR=1.78, 95% CI=1.55–2.03,  $I^2=69%$ ,  $P < .00001$ ).

### 3.3. Secondary outcome

For all-cause mortality at 90 days, all 18 included studies were analyzed. A statistically significant difference was identified between EVT and general treatment (OR=0.82, 95% CI=0.70–0.98,  $I^2=27%$ ,  $P = .03$ ) (Fig. 3). Compared to general treatment, EVT had a statistically significant but no positive effect on ICH (OR=1.28, 95% CI=1.03–1.60,  $I^2=0%$ ,  $P = .02$ ) (Fig. 4). EVT group had no advantage over the general treatment group for AIS patients in decreasing the risk of sICH (OR=1.16, 95% CI=0.85–1.57,  $I^2=0%$ ,  $P = 0.36$ ) and aICH (OR=1.43, 95% CI=1.03–1.95,  $I^2=32%$ ,  $P = 0.02$ ) (Fig. 4).

### 3.4. Subgroup analysis

**3.4.1. Max delay for intervention.** Regardless of max delay for intervention, EVT improved excellent and good functional outcomes but, by contrast, had higher rates of sICH and death. Compared with EVT, general treatment within 5 hours exhibited better effect on improving aICH (OR=1.65, 95% CI=1.10–2.45,  $P = .006$ ; Table 4). There was a modest tendency that EVT might decrease the risk of death (OR=0.78, 95% CI=0.61–1.00,  $P = .05$ ; Table 4).

**3.4.2. Stroke severity.** Stroke severity from stroke onset did not affect EVT to improve functional outcome, and patients whose NIHSS was beyond 20 have lower rate of death in EVT group (OR=0.77 95% CI=0.61–0.98,  $P = .03$ ; Table 4). However, the low stroke severity subgroup had lower risk of aICH in control group (OR=1.55, 95% CI=1.09–2.22,  $P = .02$ ; Table 4).

**3.4.3. Age.** No matter whether patients were over 70 years old or not, those who received EVT might get better functional outcome. Age did not affect the effect of EVT and general treatment on ICH. In addition, the risk of death decreased in EVT group when patients were not over 70 years old (OR=0.75, 95% CI=0.58–0.97,  $P = .03$ ; Table 4).

**3.4.4. With/without MT.** EVT can improve functional outcomes with or without MT. But only with MT, can EVT significantly decrease risk of aICH (With MT: OR=0.19, 95% CI=0.09–0.37,  $P < .00001$ ; Without MT: OR=1.65, 95% CI=1.10–2.45,  $P = .01$ ; Table 4).

### 3.5. Sensitivity analysis

Sensitivity analysis was performed by omitting one study by turns, which showed that Broderick et al<sup>[9]</sup> and Ciccone et al<sup>[11]</sup> had a great influence on the pooled ORs (Fig. 5).

### 3.6. Publication bias

No potential publication bias among the 18 included studies was noted in this meta-analysis when assessed qualitatively and quantitatively with funnel graphs (Fig. 6) and Begg test (Table 5), respectively.

## 4. Discussion

This study analyzed 18 RCTs comprising 3831 patients to evaluate the outcome in patients who were diagnosed with stroke by imaging examination and who received either EVT or general treatment. This meta-analysis was aimed at summarizing the

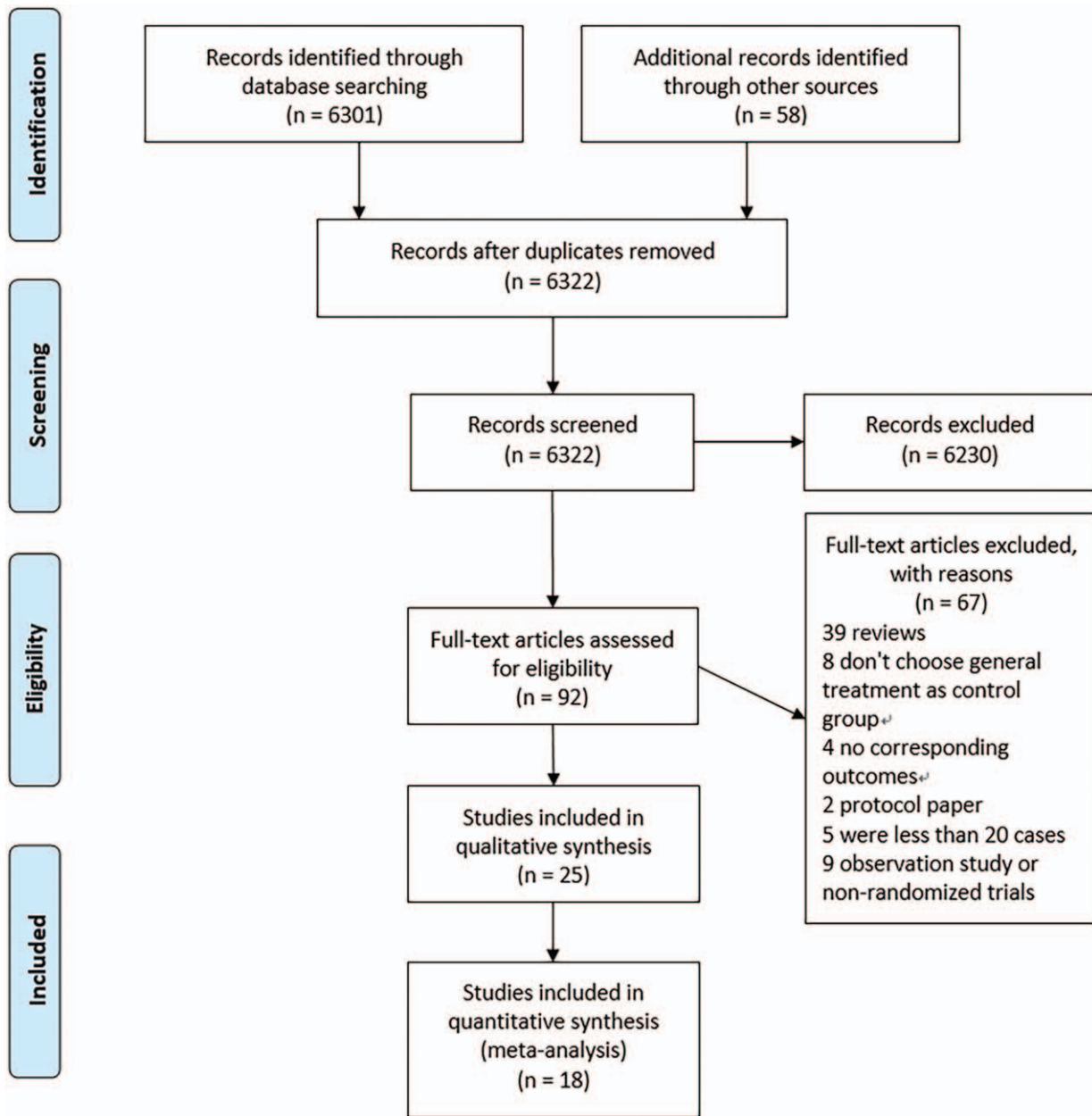


Figure 1. Study search and selection flow diagram.

benefits of EVT and exploring underlying indications of EVT for AIS patients. A total of 553 of 1885 patients (29.3% versus [vs] 19.6%) with EVT obtained excellent outcome at 90 days, and 919 of 2022 patients (45.5% vs 31.6%) with EVT achieved good outcome. Notably, the results of mRS score demonstrated that EVT resulted in improved mRS and higher likelihood of functional independence at 90 days, compared to general treatment. Furthermore, there was a tendency that patients who were randomized to receive EVT had greater chance of showing a significant decrease in the rate of all-cause mortality (16.9% vs 19.2%) compared to those who were randomized to receive general treatment. This study showed no significant difference in sICH at 90 days ( $P=.36$ ) but the other way around in aICH ( $P=.02$ ). Taken together, these results showed strong implications for the development and exploration of EVT, and

they also suggested that EVT, which serves as a crucial treatment strategy, enabled patients to recover after stroke.

It is an inaccurate belief that minor or mild stroke with low NIHSS scores is closely related to good functional outcomes. Accumulating studies demonstrated that patients with minor or mild stroke were more likely to suffered from poor functional outcomes and high rate of mortality.<sup>[31–34]</sup> Actually, AIS with low NIHSS score, defined as minor or mild stroke, appeared to be accompanied with large vessel occlusions (LVO). The STOP Stroke Study, a prospective imaging-based study of stroke outcomes, included 735 patients (mean NIHSS, 7.6), and reported that LVO was associated with negative predictions of functional outcomes (OR=0.33; 95% CI=0.24–0.45;  $P<.001$ ) and 6-month mortality (OR=4.5; 95% CI=2.7–7.3;  $P<.001$ ).<sup>[35]</sup> Zhu et al<sup>[36]</sup> found that 51 patients with severe



**Table 1**  
**Characteristics of studies included in the present meta-analysis.**

Study	Study period	Region	Medical trial center	Study design	Intervention	Control therapy	Max delay for intervention (h)	EVT information	Endovascular treatment (n)	Control (n)
Ciccione et al (2013) [11]	2008–2012	Italy	Not stated	RCT	IV t-PA+EVT	IV t-PA	6	IA thrombolysis; Mechanical clot disruption	181	181
Campbell et al (2015) [19]	2012–2014	Australia, NewZealand	14	RCT	IV t-PA+EVT	IV alteplase	6	Solitaire Flow restoration retrievable stent	35	35
Goyal, et al (2015) [21]	2013–2014	Canada, USA, South Korea, Europe	22	RCT	IV t-PA+EVT	IV alteplase	12	Stent retrievers; Solitaire Flow restoration	164	147
Jovin et al (2015) [22]	2012–2014	Catalonia, Spain	4	RCT	IV t-PA+EVT	IV alteplase	4	Stent retrievers; Solitaire Flow restoration	103	103
Jeffrey et al (2015) [25]	2012–2014	USA, Europe	39	RCT	IV t-PA+EVT	IV t-PA	6	Stent retriever; Retrievable	98	93
Broderick et al (2013) [9]	2006–2012	USA, Canada, Australia, Europe	58	RCT	IV t-PA+EVT	IV t-PA	5	Solitaire Flow restoration Merci retriever; Solitaire Flow Restoration; IA t-PA	415	214
Rai et al (2013) [24]	Not stated	Not stated	Not stated	RCT	IV t-PA+EVT	IV alteplase	3	IA thrombolysis; Mechanical thrombectomy	123	100
Serdar et al (2014) [12]	Not stated	Not stated	Not stated	RCT	IV rt-PA and/or intraarterial IA rt-PA and/or mechanical thrombectomy	IV rt-PA	4.5	Mechanical thrombectomy; IA thrombolysis; Stent retriever	14	16
Kidwell et al (2013) [14]	2004-2011	USA	22	RCT	EVT	IV t-PA	8	Mechanical embolectomy	64	54
Ciccione et al (2010) [10]	Not stated	Not stated	Not stated	RCT	EVT+IV t-PA	IV alteplase	6	Mechanical embolectomy	25	29
Berkhemer et al (2015) [18]	2010-2014	Europe	16	RCT	IA thrombolysis+ IV-tPA	IV alteplase	6	Mechanical embolectomy; Stent retriever	233	267
Ogawa et al (2007) [17]	2002-2005	Japan	57	RCT	Mechanical disruption+IA urokinase	IV t-PA	6	Mechanical disruption; IA urokinase	57	57
Qureshi et al (2017) [23]	Not stated	Not stated	Not stated	RCT	IV t-PA+EVT	IV rt-PA	6	Mechanical thrombectomy	34	17
Khoury et al (2017) [13]	2013-2014	Canada	1	RCT	IV t-PA+EVT	IV t-PA	6	Mechanical thrombectomy	40	37
Bracard et al (2016) [8]	2010-2015	French	26	RCT	IV alteplase+EVT	IV alteplase	4	Mechanical thrombectomy; IA alteplase	200	202
Mocco et al (2016) [15]	2012-2014	USA, Germany	36	RCT	IV alteplase +EVT	IV alteplase	6	Aspiration thrombectomy	62	43
Nogueira et al (2018) [20]	2014-2017	USA, Canada, Europe, Australia	26	RCT	IV t-PA+ thrombectomy	IV t-PA	24	Thrombectomy	107	99
Albers et al (2018) [16]	Not stated	USA	38	RCT	IV t-PA+ thrombectomy	IV t-PA	4.5	Thrombectomy	92	90

EVT = endovascular treatment, IA = intra-arterial, IV = intravenous, Max = maximum, RCT = randomized controlled trials.

**Table 2**  
**Characteristics of patients included in the randomized controlled trials.**

Study	Endovascular Treatment				General Treatment			
	Patients, N	Male, N	Age, yr (IQR or ± SD)	NIHSS Score (IQR or ± SD)	Patients, N	Male, N	Age, yr (IQR or ± SD)	NIHSS Score (IQR or ± SD)
Ciccone et al (2013) [11]	181	106	66 ± 11	13 (9–17)	181	103	67 ± 11	13 (9–18)
Campbell et al (2015) [19]	35	17	68.6 ± 12.3	13 (13–20)	35	17	70.2 ± 11.8	13 (9–19)
Goyal, et al (2015) [21]	164	78	71 (60–81)	16 (13–20)	147	68	70 (60–81)	17 (12–20)
Jovin et al (2015) [22]	103	55	65.7 ± 11.3	17 (14–20)	103	54	67.2 ± 9.5	17 (12–19)
Jeffrey et al (2015) [25]	98	54	65.0 ± 12.5	17 (13–20)	93	45	66.3 ± 11.3	17 (13–19)
Broderick et al (2013) [9]	415	218	69 (23–89)	17 (7–40)	214	122	68 (23–84)	16 (8–30)
Rai et al (2013) [24]	123	59	68.6 ± 16.4	16.1 ± 7.3	100	39	76.1 ± 12.7	16.1 ± 8
Serdar et al (2014) [12]	14	7	62 (54–69)	19 (15–22)	16	7	81 (74–88)	18 (14–21)
Kidwell et al (2013) [14]	64	30	66.4 ± 13.2	17 (13–21)	54	27	69.4 ± 15.9	16 (11–18)
Ciccone et al (2010) [10]	25	19	60.6 ± 13.7	17 (11–19)	29	23	64 ± 11.7	16 (12–19)
Berkhemer et al (2015) [18]	233	135	65.8 (54.5–76.0)	17 (14–21)	267	157	65.7 (55.5–76.4)	18 (14–22)
Ogawa et al (2007) [17]	57	37	66.9 ± 9.3	14.0 ± 8.0	57	37	67.3 ± 8.5	14.0 ± 6.8
Qureshi et al (2017) [23]	34	16	71 (23–81)	16 (7–25)	17	12	73 (53–81)	14 (8–24)
Khoury et al (2017) [13]	40	18	74 (62.7–80)	18 (13–22)	37	20	71 (59–79)	20 (12–23)
Bracard et al (2016) [8]	200	116	66 (54–74)	18 (15–21)	202	104	68 (54–75)	17 (13–20)
Mocco et al (2016) [15]	62	Not stated	Not stated	Not stated	43	Not stated	Not stated	Not stated
Nogueira et al (2018) [20]	107	42	69.4 ± 14.1	17 (13–21)	99	51	70.7 ± 13.2	17 (14–21)
Albers et al (2018) [16]	92	46	70 (59–79)	16 (10–20)	90	44	71 (59–80)	16 (12–21)

IQR = inter-quartile range, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation.

NIHSS patients had significantly more favorable outcome compared with those with LVO (49.0% vs 27.9%,  $P = .021$ ). There was no significant interaction between LVO and stroke severity on favorable outcome ( $P = .906$ ). These studies came to a consistent conclusion that LVO were independent from stroke severity, and LVO were closely related to poor functional outcomes and high rate of mortality.<sup>[34–36]</sup> Hence, appropriate treatment measures are dependent on the situation of cerebral vessel occlusion rather than the stroke severity. In subgroup meta-analysis, results suggested that EVT improved survival rate of patients with NIHSS scores  $\geq 20$ . However, it also uncovered a trend that EVT might deteriorate aICH for patients with NIHSS

scores  $< 20$ . Further researches on the cause of ICH and how to avoid ICH are needed to excavate, which can guide EVT to better treat patients. It is debated whether MT is associated with a higher risk of ICH. Some studies indicated that MT resulted in higher risk of sICH,<sup>[37,38]</sup> but others suggested the situation rather than just the other way around.<sup>[39,40]</sup> In subgroup analysis, it suggested that MT had little effect on the occurrence of sICH, which was not in accordance with other studies. This may be due to the other various EVT information accompanied with MT in included studies. In addition, patients with LVO stroke treated with intravenous thrombolysis alone were often accompanied with a low recanalization rate.<sup>[41]</sup> EVT is focused on relieving

**Table 3**  
**Cochrane assessment of bias risk of randomized controlled trials.**

Study	Randomization sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Ciccone et al (2013) [11]	Low	High	Low	Low	Low	Low	High
Campbell et al (2015) [19]	Low	Low	Low	Unclear	Low	Low	Low
Goyal, et al (2015) [21]	Low	Low	Low	Low	Unclear	Low	Low
Jovin et al (2015) [22]	Low	Low	Low	Low	Low	Unclear	Low
Jeffrey et al (2015) [25]	Low	Low	Low	Low	Low	Low	Low
Broderick et al (2013) [9]	Unclear	Low	Unclear	Low	High	Low	Low
Rai et al (2013) [24]	Low	Low	Low	Low	High	Low	Low
Serdar et al (2014) [12]	Low	Low	Low	Low	Low	Low	Low
Kidwell et al (2013) [14]	Low	Low	Low	Low	Low	Low	Low
Ciccone et al (2010) [10]	Low	Low	Low	Low	Low	Unclear	Unclear
Berkhemer et al (2015) [18]	Low	Low	Low	Low	Low	Low	Unclear
Ogawa et al (2007) [17]	Low	Low	Low	Low	Low	Low	Low
Qureshi et al (2017) [23]	Low	Low	Low	Low	Low	Low	Low
Khoury et al (2017) [13]	Low	Low	Low	Low	Low	Low	Low
Bracard et al (2016) [8]	Low	Low	Low	Low	Low	Low	Unclear
Mocco et al (2016) [15]	Low	Low	Low	Unclear	Low	Low	Low
Nogueira et al (2018) [20]	Low	Low	Low	Low	Low	Low	Low
Albers et al (2018) [16]	Low	Low	Low	Low	Low	Low	Low

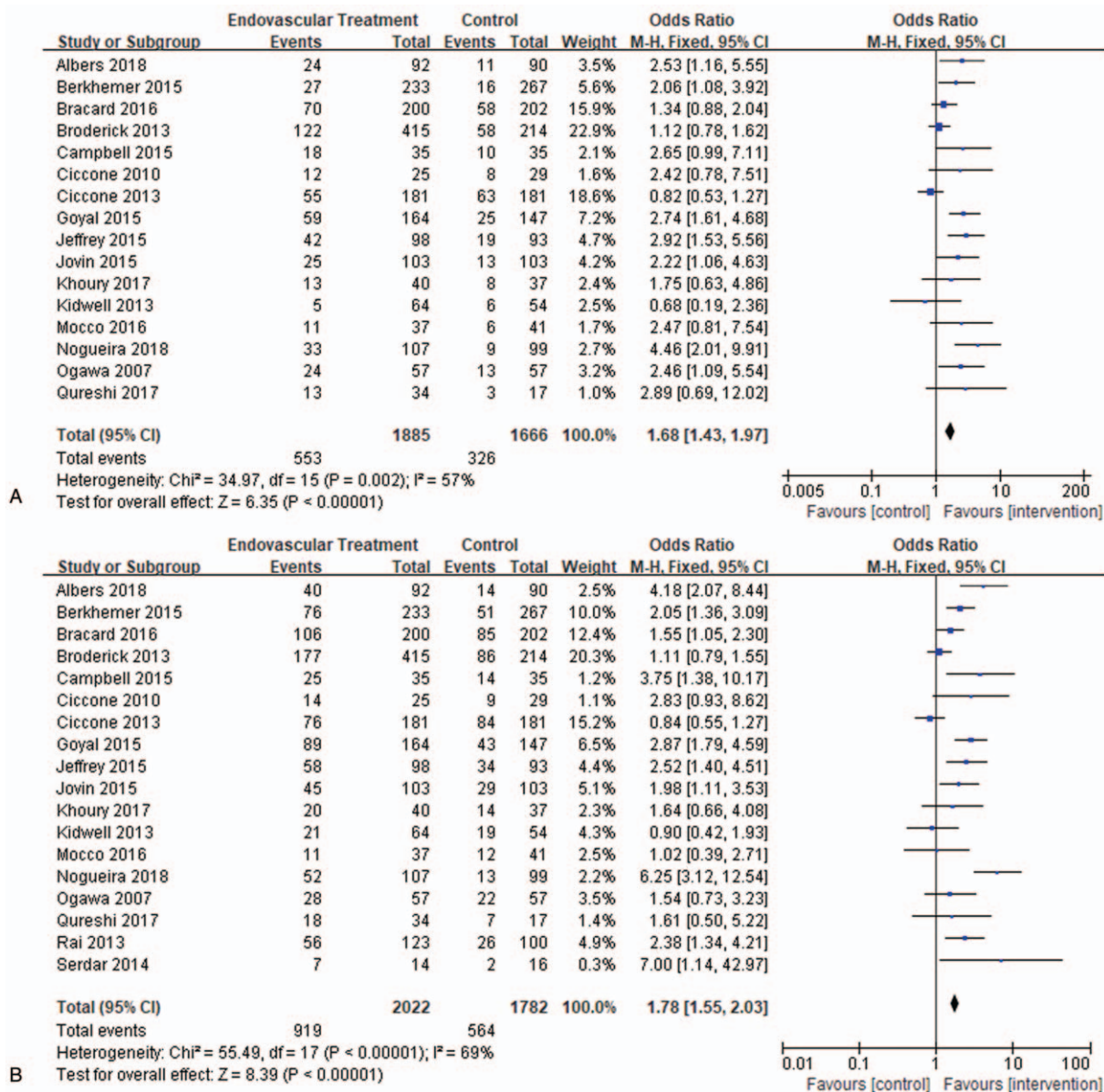


Figure 2. Forest plot of (A) mRS 0–1 (excellent outcome) and (B) mRS 0–2 (good outcome) in the intervention and control groups.

vessel occlusion and is associated with improved functional outcomes and cerebral microcirculation. Moreover, aICH, considered as indicative of microangiopathy, is a specific marker for previous bleeding from pathologically fragile cerebral small vessels. Therefore, the subgroup analysis on aICH uncovered a novel discovery that MT can effectively reduce the occurrence of aICH. Simultaneously, EVT often involves in larger doses of IV t-PA and cerebral hyperperfusion might result in poor clinical outcomes, so that the risk of sICH and mortality increased.<sup>[42,43]</sup> However, EVT with MT appeared to have no negative effects on the risk of sICH and survival rate in subgroup analysis. Compared to general treatment, the subgroup analysis on max delay for intervention showed a modest tendency that EVT was more effective and safer for stroke patients whose max delay for intervention were beyond 5 hours. Patients with age <70 appeared to have better survival rate in EVT group, which was inconsistent with some studies.<sup>[14,23,24,44]</sup> In fact, these

studies were relatively small sample sizes in paralleled with this meta-analysis. Hilditch et al<sup>[44]</sup> included 860 patients aged 80 years or older who were treated with EVT for AIS. Pooled data demonstrated that octogenarians treated with EVT had better chances of obtaining an improved functional outcome, compared with patients not treated with EVT. However, outcomes of octogenarians were still inferior to those reported for younger patients. In addition, Goyal et al.<sup>[45]</sup> included 5 RCTs of EVT, and reported good functional outcomes in 46% of patients and a mortality rate of 15%. However, among patients who were over 80 years in the EVT group, the rates were 29.8% for good functional outcome and 28% for mortality at 90 days. Another study show that there was no significant difference in sICH between octogenarians and younger patients (P = .32), whereas octogenarians had a lower rate of good clinical outcome (24% vs 48%; P = .008) and a higher rate of mortality (36% vs 12%; P = .0013).<sup>[46]</sup> Patient selection should be identified by various



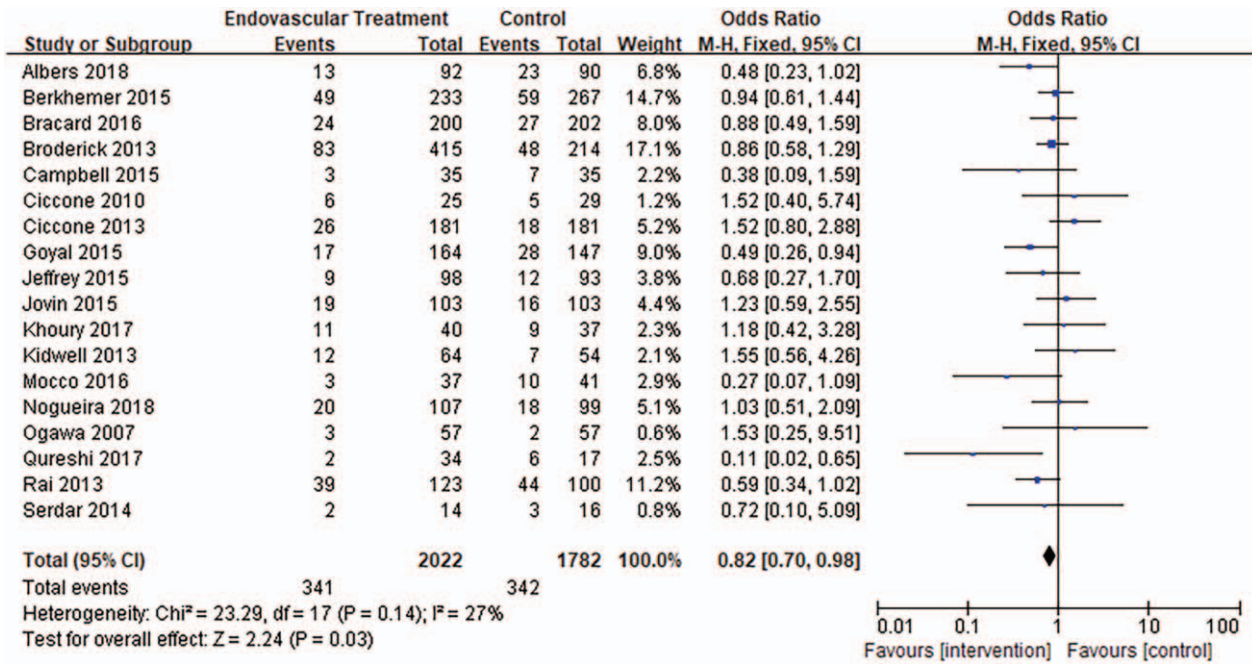


Figure 3. Forest plot of all-cause mortality in the intervention and control groups.

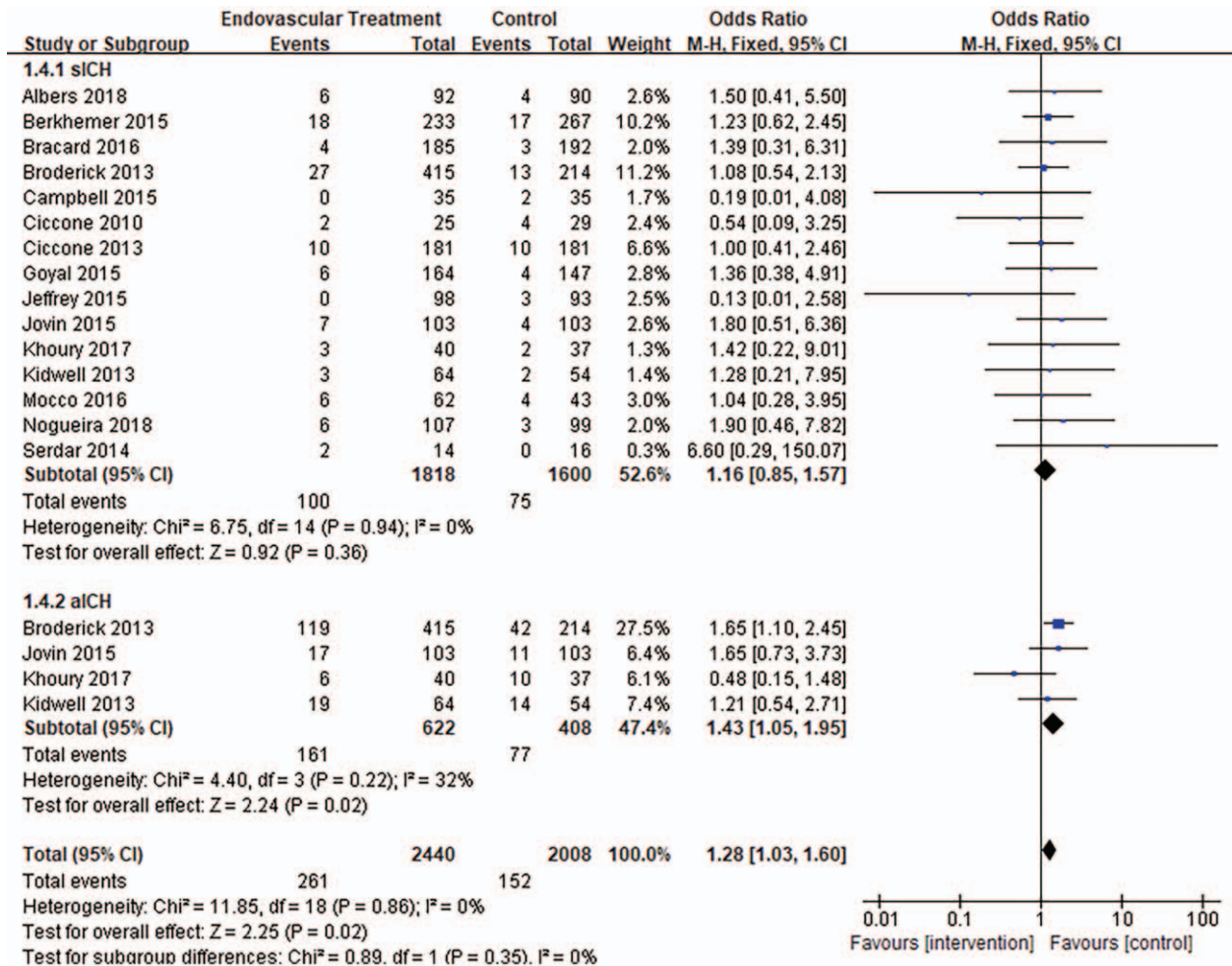


Figure 4. Forest plot of the subgroup meta-analysis of sICH and aICH in the intervention and control groups.



**Table 4**  
**Subgroup analysis of endovascular treatment and general treatment in primary outcomes and secondary outcomes.**

	Primary outcomes			
	Excellent outcome		Good outcome	
	OR (95% CI)	P value	OR (95% CI)	P value
Max delay for intervention (hours)				
Time >5h	1.81 (1.43, 2.30)	<.00001	1.90 (1.59, 2.27)	<.00001
Time ≤5h	1.40 (1.09, 1.79)	.007	1.67 (1.36, 2.04)	<.00001
Stroke severity at baseline				
NIHSS ≥20	1.90 (1.47, 2.46)	<.00001	2.06 (1.69, 2.51)	<.00001
NIHSS <20	1.53 (1.24, 1.88)	<.0001	1.75 (1.45, 2.12)	<.00001
Age (years)				
Age ≥70	1.47 (1.18, 1.84)	.0007	1.61 (1.34, 1.92)	<.00001
Age <70	1.91 (1.51, 2.42)	<.00001	2.05 (1.66, 2.53)	<.00001
With/without MT				
With	1.56 (1.26, 1.93)	<.0001	1.81 (1.52, 2.15)	<.00001
Without	1.54 (1.17, 2.09)	.003	1.49 (1.14, 1.94)	.003

	Secondary outcomes					
	aICH		sICH		Death	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Max delay for intervention (hours)						
Time >5h	0.99 (0.58, 1.69)	.69	0.88 (0.46, 1.68)	.81	0.86 (0.68, 1.09)	.22
Time ≤5h	1.65 (1.10, 2.45)	.006	1.65 (1.15, 2.36)	.24	0.78 (0.61, 1.00)	.05
Stroke severity at baseline						
NIHSS ≥20	1.08 (0.57, 2.04)	.82	1.30 (0.88, 1.91)	.18	0.77 (0.61, 0.98)	.03
NIHSS <20	1.55 (1.09, 2.22)	.02	0.97 (0.54, 1.76)	.93	0.92 (0.72, 1.18)	.52
Age (years)						
Age ≥70	1.41 (0.80, 2.51)	.24	1.09 (0.71, 1.67)	.71	0.83 (0.66, 1.04)	.11
Age <70	1.30 (0.90, 1.88)	.16	1.45 (0.76, 2.76)	.26	0.75 (0.58, 0.97)	.03
With/without MT						
With	0.19 (0.09, 0.37)	<.00001	1.27 (0.84, 1.90)	.25	0.88 (0.71, 1.09)	.26
Without	1.65 (1.10, 2.45)	.01	0.86 (0.49, 1.50)	.59	0.73 (0.52, 1.03)	.07

aICH = asymptomatic intracerebral hemorrhage, CI = confidence interval, MT = mechanical thrombectomy, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, sICH = symptomatic intracerebral hemorrhage.

factors, especially when considering octogenarians for EVT. Taken together, these results were comparable with those obtained by our meta-analysis of 18 included studies.

ICH accounts for approximately 10% to 30% of stroke patients and results in high rates of mortality and functional disability among survivors.<sup>[47]</sup> Inflammation is one of the main pathogenetic factors in ischemic stroke.<sup>[48,49]</sup> Ischemia and reperfusion injury triggered both the production and secretion of inflammatory cytokines and pro-inflammatory cytokines. Early inflammation may be detrimental on the functional outcome. Reactive microglia/macrophages can be observed as early as 2 hours after an ischemic stroke and maintained for up to 1 week.<sup>[50]</sup> Following activation of peripheral leukocytes and infiltration into the brain, the tight junctions between endothelial cells of the Blood-brain barrier are disrupted and become more permeable.<sup>[51-53]</sup> Blood-brain barrier disruption has been suggested as an underlying mechanism for ICH after ischemic stroke.<sup>[54]</sup> ICH poses a safety concern for EVT, and even may decrease the benefit-risk ratio of EVT. Therefore, it is vital to identify appropriate predictors to evaluate the incidence of ICH after EVT. Accumulating evidences showed that neutrophil-to-lymphocyte ratio (NLR) was associated with an increased risk of ICH and outperformed other predictors.<sup>[55-58]</sup> Lattanzi et al.<sup>[58]</sup> included 177 patients and reported that higher neutrophils (OR = 1.22, 95% CI = 1.03-1.44, P = .023) and lower lymphocytes (OR = 0.57, 95% CI = 0.33-0.99, P = .046) independently associated with poor ICH outcome. A prospective study (n = 58

including 28 thrombolytic patients, 10 patients subjected to thrombectomy following thrombolysis, and 20 patients assigned to no causal treatment) reported significantly high NLR in those treated with thrombolysis and thrombectomy compared to the other groups (P = .03).<sup>[59]</sup> The results might be related to increased severity of the disease in these patients. However, the relationship between the severity of inflammation, evidenced by increased NLR, and the outcome of stroke treatment remains vague and worth exploring. Overall, NLR played a vital role in the risk stratification of AIS patients for EVT and decreasing risk of ICH after EVT.

In view of medium heterogeneity in excellent outcome (mRS 0-1) and good outcome (mRS 0-2), sensitivity analysis was performed. After excluding Broderick et al.<sup>[9]</sup> and Ciccone et al.<sup>[11]</sup> from the meta-analysis of excellent outcome, I<sup>2</sup> changed from 57% to 7%. In Broderick et al.<sup>[9]</sup>, loss to follow-up and unrandomized grouping (participants without angiographic evidence of a treatable occlusion received no additional treatment, but those with a treatable vascular occlusion received EVT) might cause heterogeneity. In Ciccone et al.<sup>[11]</sup>, no patient was lost to follow-up and dropped out of the trial, whereas 15 of the 181 patients randomized to EVT group did not receive the treatment, which might result in heterogeneity. Moreover, when Broderick et al.<sup>[9]</sup>, Ciccone et al.<sup>[11]</sup>, Albers et al.<sup>[16]</sup> and Nogueira et al.<sup>[20]</sup> were excluded, I<sup>2</sup> changed from 69% to 15%. Only partial patients who present within 6 to 24 hours after the onset of stroke may meet the imaging-based eligibility criteria., which

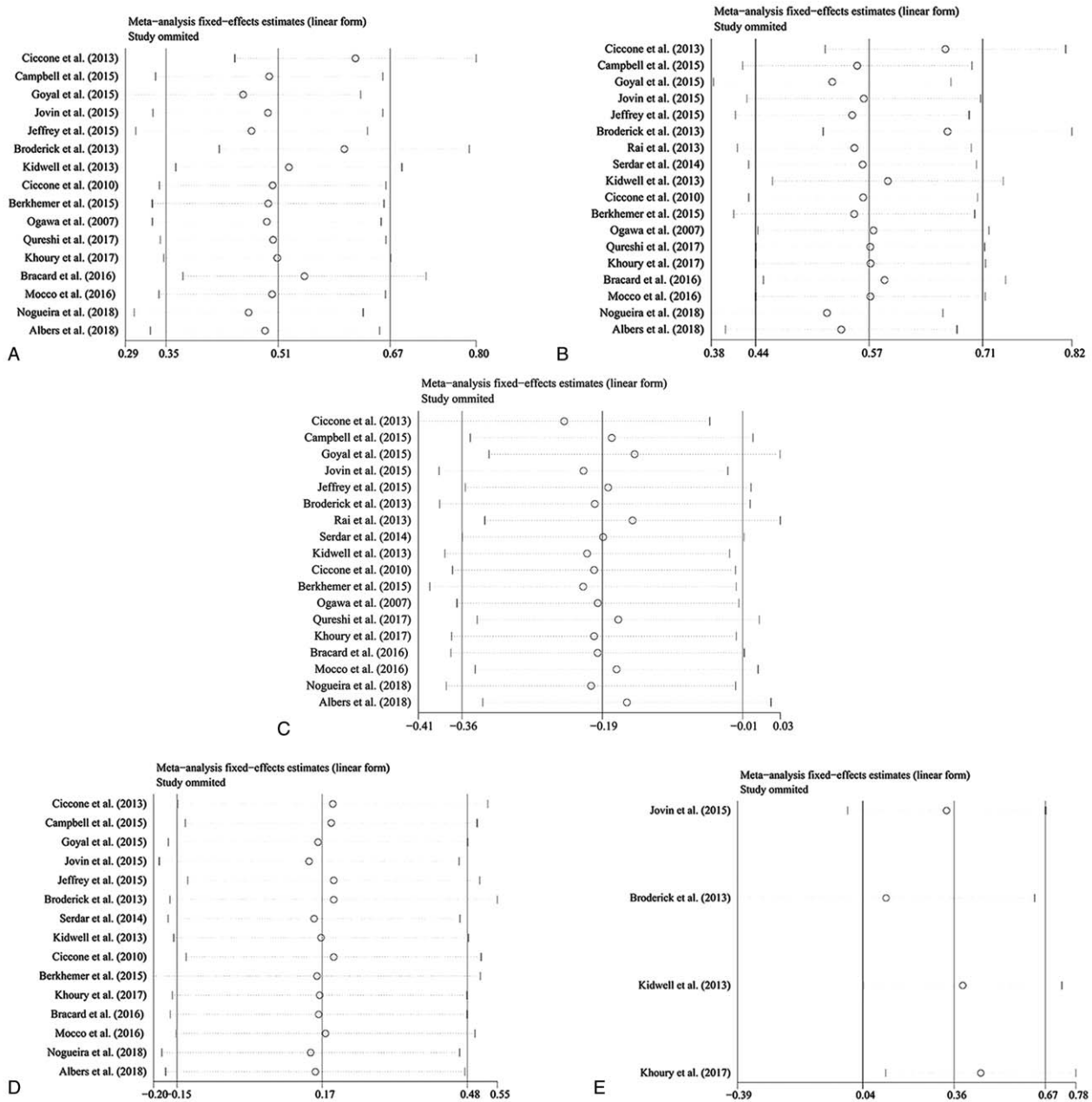


Figure 5. Forest plot in the sensitivity analysis of (A) mRS 0–1, (B) mRS 0–2, (C) all-cause mortality, (D) sICH and (E) aICH in AIS.

might account for the heterogeneity caused by Albers et al<sup>[16]</sup> Nogueira et al<sup>[20]</sup> enrolled patients with larger core infarctions than other trials and also included patients with milder stroke symptoms.

Before 2015, there has been some controversy about the superiority of EVT for the treatment of stroke. Based on accumulating trials, the mainstream view about the value of EVT was that EVT is not superior to general treatment.<sup>[8–15]</sup> Furthermore, the mainstream view was confirmed by results of meta-analyses.<sup>[60,61]</sup> As opposed to prior meta-analyses, some subsequent meta-analyses justified the superiority of EVT for stroke after 2015.<sup>[60,62–65]</sup> However, the justification of benefits was just limited to improvement of functional outcomes and functional independence.

Previous meta-analyses were performed with small samples, no more than 1500 cases, which appeared to have negative effects on the comparison between EVT and general treatment. In this meta-analysis, a comprehensive database search was performed, and as a result, 18 studies comprising a total of 3831 patients were included. As a large number of cases were included in the analysis, which was rare in other meta-analyses, there was a significant decrease in heterogeneity compared with that in other meta-analyses. Tan et al.<sup>[65]</sup> merged trials of IA thrombolysis with MT, but the recanalization rate of MT can reach to 70%, while IA thrombolysis is only about 20%. Therefore, it appeared to be inappropriate to merge trials of IA thrombolysis with MT, and we excluded trials of IA thrombolysis in this meta-analysis. Low or no heterogeneity ensured that this meta-analysis was

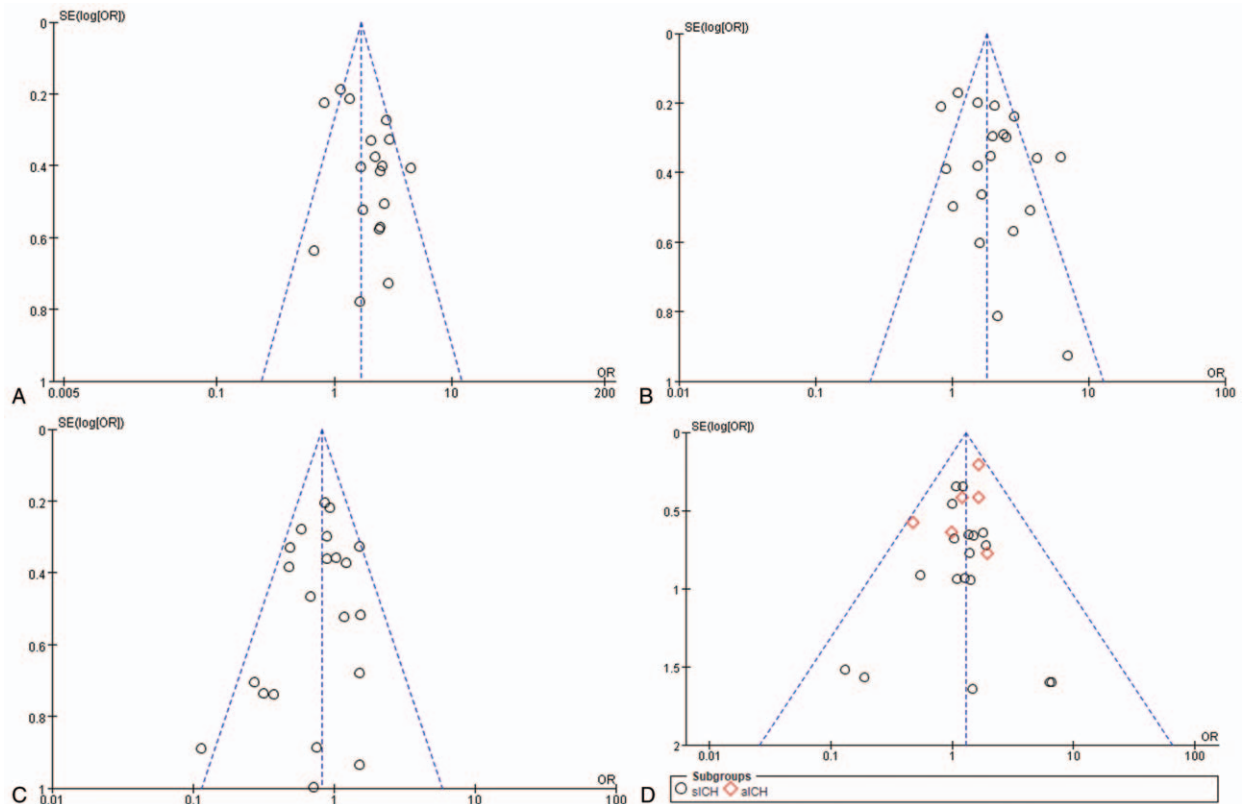


Figure 6. Funnel graph of all outcomes. (A) mRS 0–1, (B) mRS 0–2, (C) all-cause mortality, (D) sICH and aICH.

sufficiently reliable. In addition, EVT significantly reduced the odds of all-cause mortality, which was not found in previous meta-analyses. This analysis was novel, as not only sICH but also aICH was selected as a secondary outcome to perform subgroup analysis. Unfortunately, aICH was considered as a non-significant outcome in previous meta-analyses, but it was placed an indispensable importance in this meta-analysis. Compared to general treatment, our results showed that sICH were not improved by EVT according to the results of this meta-analysis, and a higher rate of aICH was found in patients treated with EVT. It demonstrated that the increasing risk of aICH was the main cause of significantly higher risk of ICH in patients treated with EVT, which was not found in previous meta-analyses. From the perspective of pooled outcomes and subgroup analysis, EVT might entail deteriorated intracerebral hemorrhage, when the max delay for invention of patients with NIHSS<20 is within 5 hours. This meta-analysis seems to preliminarily clarify the contraindications of EVT.

The quality of the 18 included studies was generally high, and it was confirmed that there was no evidence of publication bias in this

meta-analysis. Despite the shining points of this meta-analysis, its limitations and shortcomings should be emphasized. Patients could not be blinded and this may have resulted in patients intervening in most of the trials, which may have led to performance bias. Data were extracted from trials with impossibly different designs, in particular with respect to patient enrollment, time to treatment, different drug dosages, and devices, which may have led to diverse biases. Moreover, these included trials had the following notable shortcomings: misdraw, use of different MT devices, and diverse uses of IV t-PA as an adjunct in EVT. In addition, results were incomplete in this meta-analysis. EVT was focused on relieving vessel occlusion and increased the likelihood of recanalization in stroke. Due to the absence of available data in included studies, it was arduous to stratify outcomes on the basis of recanalization rate, stroke onset-to-recanalization time and type of anesthesia used, which devastatingly affected this meta-analysis to further explore underlying indications of EVT for AIS. Meanwhile, the EVT prognosis of patients with NIHSS≤5 could not be performed to obtain, which was widely recognized as mild ischemic stroke.

**Table 5**  
Effect of endovascular treatment on the end points obtained from all 18 included studies.

End points	Number of trials	Intervention, n/N (%)	Control, n/N (%)	Pooled OR (95% CI)	Test for publication bias (Begg test)	P value	I <sup>2</sup>
mRS 0–1	16	553/1885 (29.3%)	326/1666 (19.6%)	1.68 (1.43–1.97)	0.964	<.00001	57%
mRS 0–2	18	919/2022 (45.5%)	564/1782 (31.6%)	1.78 (1.55–2.03)	0.256	<.00001	69%
All-cause mortality	18	341/2022 (16.9%)	342/1782 (19.2%)	0.82 (0.70–0.98)	0.649	=.03	27%
sICH	15	100/1818 (5.5%)	75/1600 (4.7%)	1.14 (0.85–1.57)	0.692	=.36	0%
aICH	4	161/622 (25.9%)	77/408 (18.9%)	1.41 (1.03–1.95)	0.308	=.02	32%

aICH = asymptomatic intracerebral hemorrhage, mRS = modified Rankin Scale, n/N = number of patients achieving each end point/number of patients included, OR = odds ratio, sICH = symptomatic intracerebral hemorrhage.

Therefore, the relationship between minor or mild stroke and poor clinical outcomes could not be further presented in this meta-analysis.

Time to recanalization is the major limitation of EVT. It was noted that ESCAPE [22] showed the maximum delay time for recanalization, whereas further trials with positive results showed time to treatment from 3 to 5 hours. Based on computed tomography, a retrospective study reported that a novel EVT might reduce the time to treatment.<sup>[66]</sup> Also, rapid transfer of patients and popularization of stent retrievers can shorten the treatment time, which may be a research hotspot for exploration and development in the near future.

## 5. Conclusion

In conclusion, this meta-analysis provides some evidences for improved functional outcome and decreased odds of all-cause mortality following EVT compared with that following general treatment after 90 days from stroke onset. However, EVT might lead to higher risk of ICH, which hampers the application and development of EVT. Moreover, EVT with MT can reduce the occurrence of aICH in AIS patients. Furthermore, this meta-analysis supports currently EVT as a treatment strategy to improve the clinical outcomes in AIS patients with age <70, NIHSS $\geq$ 20 and max delay for intervention >5 hours, who may benefit the most from EVT. Also, it suggests that “with mechanical thrombectomy” is potential favorable factor for improving aICH in comparison with general treatment. General treatment can play a vital role in clinical treatment of AIS patients through the supplement of EVT. In the near future, RCTs should be devote to providing more data regarding the potential association of EVT with the risk of aICH.

## Acknowledgments

We thank LetPub ([www.letpub.com](http://www.letpub.com)) for its linguistic assistance during the preparation of this manuscript.

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