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Endovascular Treatment Versus Intravenous Thrombolysis for Acute Ischemic Stroke: a Quantitative Review and Meta-Analysis of 21 Randomized Trials

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Abstract Emerging studies suggest that endovascular treatment (EVT) may be superior to intravenous thrombolysis for acute ischemic stroke (AIS). We performed a systematic review and meta-analysis of all randomized controlled trials (RCTs) to assess the efficacy and safety of endovascular treatment in patients with acute ischemic stroke as compared with intravenous thrombolysis. We assessed RCTs investigating EVT versus intravenous thrombolysis (IVT) published up to June 2015. In total, 21 studies of 4473 patients were included in the systematic review and meta-analysis. EVT significantly improved functional outcome at 90 days (risk ratio (RR) 1.35, 95 % confidence interval (CI) 1.18 to 1.55, $I^2 = 61$ %) and reduced the mortality (RR 0.81, 95 % CI 0.68 to 0.95, $I^2 = 0$ %), with similar symptomatic hemorrhagic transformation (SHT) rate (RR 1.12, 95 % CI 0.88 to 1.44, $I^2 = 0$ %). Based on the current data, endovascular therapy may produce good clinical outcomes with similar symptomatic hemorrhage and mortality as compared with intravenous thrombolysis in acute ischemic stroke. This advancing intervention is a landmark change in stroke treatment and could be of huge potential benefit to patients worldwide.

Keywords Acute ischemic stroke · Endovascular treatment · Intravenous thrombolysis · Systematic review · Meta-analysis

Introduction

Approximately 795,000 Americans each year experience a new or recurrent stroke. Of all strokes, 87 % are ischemic type, which is one of the leading causes of mortality and morbidity in the world [1]. As a systemic treatment, intravenous (IV) thrombolysis with a recombinant tissue plasminogen activator (tPA) is recommended for acute ischemic stroke (AIS) within 4.5 h of symptom onset [2]. However, the low recanalization rates and relatively short therapeutic time window after symptom onset with IV tPA promoted the exploration of endovascular treatment (EVT) in AIS [3] .

Acute endovascular reperfusion is becoming an important part of acute ischemic stroke therapy and has been the focus of recent randomized clinical trials. As compared with intravenous thrombolysis, endovascular treatment is associated with a higher probability of recanalization [4]. Moreover, PROACT [5], ESCAPE [6], and REVASCAT [7] trials supported that rapid endovascular treatment improved functional outcomes and reduced mortality. However, the previous randomized controlled trials (RCTs) have showed opposite results [8–11]. The inconsistent results from these trials confused neurologists. Thus, we performed a systematic review and meta-analysis of all randomized controlled trials (RCTs) to assess the efficacy and safety of endovascular treatment in patients with acute ischemic stroke as compared with intravenous thrombolysis.

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Methods

Search Strategy

We searched PubMed (1966 to June, 2015) and EMBASE (1980 to June, 2015) with the terms "acute ischaemic stroke, " "brain ischemia" or "stroke," "endovascular treatment," "intravenous thrombolysis," "tissue plasminogen activator," "stent retrievers," "thrombectomy," and "intra-arterial thrombolysis." Other sources searched were conference proceedings, abstracts, thesis dissertations, poster presentations, and materials from professional society meetings. Reviews without original data, meeting abstracts, and case reports series were excluded. Studies reporting outcomes from acute thrombolysis and endovascular treatment were included for review.

Selection Criteria and Data Retrieval

Trials that were included met the following criteria: (1) random assignment to endovascular treatment (intra-arterial thrombolysis, thrombectomy, stent retrievers, or combined treatment) or intravenous thrombolysis, (2) inclusion of patients who have a diagnosis of acute ischemic stroke and have been ruled out the diagnosis of intracranial hemorrhage, (3) inclusion of patients who have a clearly defined time of stroke onset that allowed for immediate initiation of intravenous thrombolysis (defined as within 4.5 h after symptom onset) or for the administration of endovascular treatment as soon as possible (within 6 h after symptom onset), and (4) specification of therapy formulations. Studies with fatal flaws in study design or data analysis were excluded, as were trials whose data were not readily available.

We obtained the following baseline variables from each study: sample size, age, type of intervention, time to intervention, baseline National Institutes of Health Stroke Scale (NIHSS) score, numbers randomized, primary outcomes, adverse events, and all-cause death during the random trial. Data abstraction was accomplished under the cooperation between two investigators by use of a standardized data extraction. Any discrepant data were reviewed by discussion with other team members or contact with original investigators, who were all sent emails with requests for the exact data. For missing data (standard deviations), we sought missing information and essential clarification from the author.

The modified Rankin scale (mRS) is a tool used to measure the post-stroke functional outcome, with scores ranging from 0 to 6 (0, no symptoms at all; 1, no major disability; 2, slight disability; 3, moderate disability requiring some help but able to walk without assistance; 4, moderately severe disability; 5, severe disability; and 6, death). The primary outcome of interest for our study was mRS at 90 days. We defined good functional outcome as mRS between 0 and 2 points. Secondary outcomes were all-cause mortality and the symptomatic intracerebral hemorrhage (sICH) rate. We recorded the discontinuations from the trials to assess the benefits and risks of these treatments.

Statistical Analysis

The outcomes and the numbers of patients for each trial were statistically combined by use of the Review Manager Version 5.2 software. For dichotomous clinical outcomes, mortality, and the symptomatic ICH (sICH) rate, we conducted an analysis of the risk ratio (RR), absolute risk differences with 95 % confidence interval (CI), and P values to assess the efficacy and safety of the study treatment.

When meta-analysis is conducted, we assessed for clinical, statistical, and methodological heterogeneity. We quantitatively tested the heterogeneity between the trials using the visual inspection, and a χ^2 test combined with the I^2 method. I^2 approximates the proportion of total variation in the effect size estimates that is due to heterogeneity rather than sampling error. A α error $p < 0.20$ and an I^2 statistic greater than 50 % was taken as indicators of heterogeneity of outcomes. All analyses were two-tailed, with 5 % risk of a type I error (α of 0.05).

Results

Study Selection and Characteristics

The search strategy yielded 1305 citations in PubMed, EMBASE, International Pharmaceutical Abstracts, clinicaltrials.gov, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, and the Cochrane Cognitive Improvement Group specialized registry. Twenty-one studies met the eligibility criteria, comprising 4473 patients with AIS, of which 2252 (50.3 %) received ET with or without IV tPA and 2221 (49.7 %) received a control intervention (IV-tPA) [6–9, 12–28]. The search procedure and reasons for exclusion of other studies are shown in Fig. 1.

The included trials each required a diagnosis of acute ischemic stroke and have ruled out the diagnosis of intracranial hemorrhage. The study sample size ranged from 7 patients to 656 patients. Among these trials, four studies did not measure and report the mRS scores at 90 days [13, 18, 20, 26]. Reported baseline characteristics were similar between intervention and placebo groups in all the trials. Design and population characteristic of included trials are shown in Table 1.

Quality Assessment

The quality assessment of the included trials using the Jadad score is shown in Table 1. Performance bias was observed in

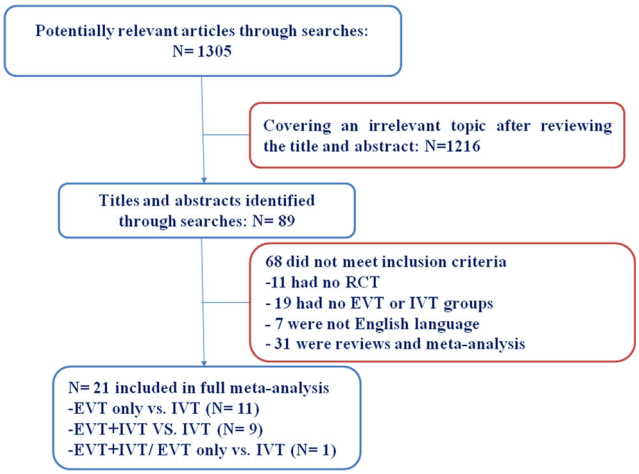

Fig. 1 Flowchart describing the approach used to identify all eligible studies of meta-analysis

all studies because none of the studies did a sham procedure in the control group.

Efficacy

There were 17 studies that measured and reported the numbers of patients with good functional outcome (mRS score between 0 and 2 points) at 90 days for EVT compared with intravenous thrombolysis (IVT). Seven trials assigned eligible patients to either EVT plus IVT or IVT alone. Nine trials assigned eligible patients with ischemic stroke to undergo either EVT or IVT. The cases in one trial received EVT plus IVT or EVT alone. Data on the primary outcome were complete. There was a shift in the distribution of the primary-outcome scores in favor of the EVT group. The risk ratio was 1.35 (95 % confidence interval [CI], 1.18 to 1.55; heterogeneity, $I^2 = 61$ %; Fig. 2).

The subgroup analysis according to the type of endovascular treatment (EVT only or EVT plus IVT) revealed the consistent results in patient outcomes (Fig. 3). We observed better functional outcome when we compared trials in which only EVT was used as the experiment group versus trials in which only IVT was used as the control group (RR 1.17, 95 % CI 1.03 to 1.33; heterogeneity, $I^2 = 59$ %). Similarly, we observed better functional outcome when we compared trials in which both IVT and EVT were used as the experiment group versus trials in which only IVT as the control group (RR 1.44, 95 % CI 1.28 to 1.61; heterogeneity, $I^2 = 61$ %).

Safety

There were 16 trials that reported the number of patients with symptomatic hemorrhagic transformation (SHT),which is defined as any hemorrhage plus a neurologic deterioration of four points or more in the NIHSS score from the baseline or from the lowest NIHSS value after the baseline, or leading to death [29]. The proportion of patients with SHT was not different when EVT was compared with IVT. The pooled proportions were 6.98 versus 6.57 % (RR 1.12, 95 % CI 0.88 to 1.44). Heterogeneity was low for overall analysis ($I^2 = 0$ %). We used the Mantel–Haenszel fixed-effects model. The detailed information is shown in Fig. 4.

The subgroup analysis according to the type of endovascular treatment (EVT only or EVT plus IVT) reveals the consistent results in patient SHT rate (Fig. 5). We observed similar SHT rate between two arms when we compared trials in which only EVT was used as the experiment group versus trials in which only IVT was used as the control group (RR 1.21, 95 % CI 0.84 to 1.75; heterogeneity, $I^2 = 0$ %). Similarly, we obtained the same result when we compared trials in which both IVT and EVT were used as the experiment group versus trials in which only IVT was used as the control group (RR 1.05, 95 % CI 0.71 to 1.55; heterogeneity, $I^2 = 0$ %).

Nineteen studies presented data on all-cause mortality. The pooled mortality was significantly greater in patients treated with IVT only group than that I patients with the EVT group. A mortality of 16.40 % was noted in the endovascular therapy group compared with 19.07 % in the intravenous thrombolysis group. We used the Mantel–Haenszel fixed-effects model. The pooled RR was 0.81 (95 % CI, 0.68 to 0.95; $P = 0.009$). Heterogeneity was also low for overall analysis ($I^2 = 0$ %). The detailed information is shown in Fig. 6. However, the subgroup analysis found that there were no differences between two arms in both subgroups (Fig. 7).

Discussion

There is general consensus based on strong evidence that in patients presenting within 4.5 h of symptom onset, intravenous recombinant tissue plasminogen activator (IV rtPA) therapy is the standard treatment for acute ischemic stroke. However, the low recanalization rates and relatively short therapeutic time window after symptom onset with IV tPA impede its clinical effectiveness. For these reasons, endovascular treatments including endovascular pharmacologic thrombolysis, manipulation of the clot with the use of a guidewire or microcatheter, mechanical and aspiration thrombectomy, and stent retriever technology have been the focus of recent randomized clinical trials [30]. However, the inconsistent results from these trials confused neurologists. Results of initial randomized trials of endovascular treatment for ischemic stroke were neutral, but strongly positive results of recent trials of endovascular thrombectomy for ischemic stroke led to widespread optimism in the neurological community about the value of endovascular treatment. Thus, we conducted this current meta-analysis including 4804 patients hospitalized for acute ischemic stroke to evaluate the efficacy

Table 1 Design and baseline characteristics of included trials

Reference (author, year)	Trial name	Type of EVT	Patients	Age mean ± SD	Sex (% men)	NIHSS score median (IQR)	Jadad score
Berkhemer et al., 2015 [12]	MR CLEAN	IVT + EVT (thrombolytic agent, mechanical thrombectomy, or both)	IVT (267) EVT (233)	65.7 65.8	58.8 57.9	18 (14–22) 17 (14–21)	5
Broderick et al., 2013 [8]	IMS III	IVT + EVT (IA delivery of reteplase/ Mechanical clot retrieval)	IVT (222) EVT (434)	68 69	55 50.2	16 17	5
Burns et al., 2008 [13]		IVT + EVT (IA delivery of reteplase/ Mechanical clot retrieval/ Clot disruption)	IVT (30) EVT (33)	66.4 ± 17.4 66.6 ± 12.0	30 33.3	16 (14–18.75) 15.8 (13–19)	4
Campbell et al., 2015 [14]	EXTEND-IA	IVT + EVT (Solitaire FR retrievable stent [Covidien])	IVT (35) EVT (35)	70.2 ± 11.8 68.6 ± 12.3	49 49	13 17	5
Ciccone et al., 2010 [15]	SYNTHESIS pilot trial	EVT (IA delivery of alteplase, if necessary with mechanical clot disruption and/ or retrieval)	IVT (29) EVT (25)	64.0 ± 11.7 60.6 ± 13.7	79 76	16 (12–19) 17 (11–19)	5
Ciccone et al., 2013 [9]	SYNTHESIS EXP	EVT (IA delivery of reteplase/ Mechanical clot retrieval/ Clot disruption)	IVT (181) EVT (181)	67 ± 11 66 ± 11	57 59	13 (9–18) 13 (9–17)	5
Ducrocq et al., 2005 [16]		EVT (IA delivery of reteplase)	IVT (14) EVT (13)	58 59.5	64.3 92.3		4
Goyal et al., 2015 [6]	ESCAPE	IVT + EVT (thrombectomy devices)	IVT (150) EVT (165)	70 71	47.3 47.9	17 (12–20) 16 (13–20)	5
IMS II, 2007 [17]	IMS II	EVT (IA delivery of rt-PA)	IVT (182) EVT (81)	64 ± 10.4 64 ± 11.5	57 56.79	18 19	5
Jovin et al., 2015 [7]	REVASCAT	IVT + EVT (Solitaire device)	IVT (103) EVT (103)	67.2 ± 9.5 65.7 ± 11.3	52.4 53.4	17 (12–19) 17 (14–20)	5
Keris et al., 2001 [18]		IVT + EVT (IA delivery of reteplase)	IVT (33) EVT (12)	65 ± 8 53 ± 9	51.5 83.3	26 25	4
Kidwell et al., 2013 [19]	MR RESCUE	EVT (Merci Retriever or Penumbra System)	IVT (54) EVT (64)	67.1 64.2	50 46.9	15 17.4	5
Macleod et al., 2005 [20]		EVT (IA delivery of urokinase)	IVT (8) EVT (8)	63.7 ± 12.3 64.2 ± 11.1	38 88	18 23	4
Mazighi et al., 2009 [21]	RECANALISE	IVT + EVT (IA delivery of alteplase)	IVT (107) EVT (53)	64.1 ± 14.2 67.9 ± 15.8	60 57	16 (11–19) 14 (10–18)	5
Min Uk Jang et al., 2014 [22]		EVT (IA delivery of reteplase/mechanical clot retrieval/clot disruption)	IVT (141) EVT (166)	70.0 ± 12.4 67.8 ± 11.1	66 96	12 (7–17.5) 16.5 (11–20)	4
Ogawa et al., 2007 [23]	MELT	EVT (IA delivery of UK)	IVT (57) EVT (57)	67.3 ± 8.5 66.9 ± 9.3	64.9 64.9	14 14	5
Paciaroni et al., 2015 [24]	ICARO-3	EVT + IVT or EVT (IA delivery of reteplase/ mechanical clot retrieval/clot disruption)	IVT (324) EVT (324)	63.5 ± 12.9 62.9 ± 13.4	63.3 63.3	16 (12–20) 16 (11–20)	5
Rai et al., 2013 [25]		EVT (IA delivery of reteplase/mechanical clot retrieval/clot disruption)	IVT (100) EVT (123)	76.1 ± 12.7 68.6 ± 16.4	39 48	16.1 16.1	4
Sen et al., 2009 [26]		EVT (IA delivery of rt-PA)	IVT (4) EVT (3)	68 ± 16	71	16	4
Strbian et al., 2012 [27]		EVT (Mechanical procedure, IA thrombolysis, or both)	IVT (82) EVT (41)	65 ± 17 65 ± 15.5	51.2 56.1	17 15	4
Saver et al., 2015 [28]	SWIFT PRIME	IVT + EVT (Solitaire FR or Solitaire 2 device)	IVT (98) EVT (98)	66.3 ± 11.3 65.0 ± 12.5	47 55	17 (13–19) 17 (13–20)	5

EVT endovascular treatment, *IVT* intravenous thrombolysis, *NIHSS* National Institute of Health Stroke Scale, *IQR* interquartile range

and safety of endovascular treatment on different outcome measures (all-cause mortality, functional outcome, and symptomatic hemorrhagic transformation [SHT] rate).

This meta-analysis combined the results from all trials to date comparing EVT to IVT. On the basis of these 21 trials, we found that EVT is superior to IVT in improving mortality and functional outcome at 3 months with a similar rate of symptomatic hemorrhage. Analysis of both EVT combined with IVT subgroup and EVT without IVT subgroup obtained consistent results in functional outcome at 3 months, without difference between the two arms in mortality and symptomatic hemorrhagic transformation rate.

Two years ago, the mainstream view in the neurological community about the value of endovascular treatment is that

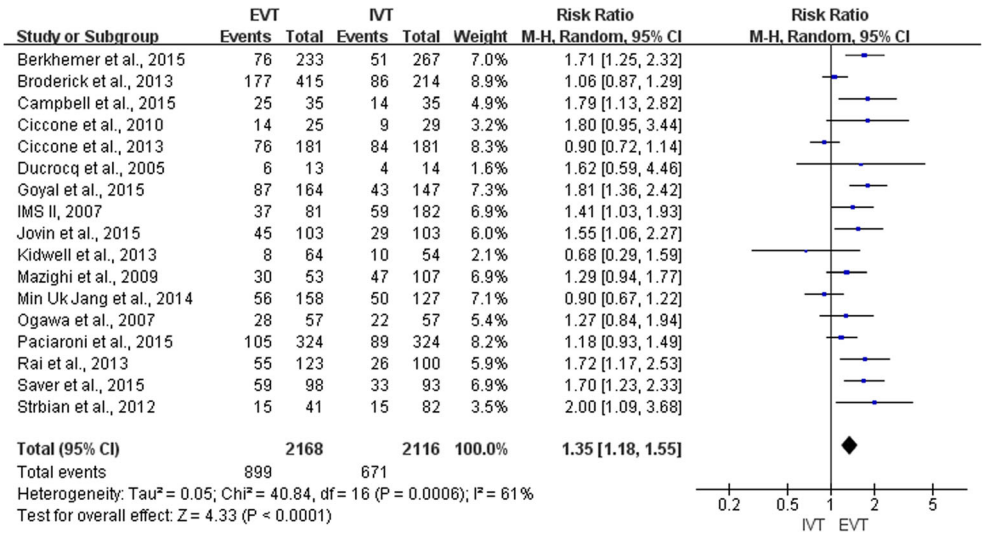

Fig. 2 Functional outcomes (mRS score between 0 and 2 points) at 90 days for EVT compared with IVT

EVT is not superior to IVT, which is supported by the famous SYNTHESIS EXP trial [9] and verified by two meta-analysis [31, 32]. Recently, positive randomized trials including Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) [28], Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) [14], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) [6], Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) study [12], and Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) [7] have now been published. All these high-quality trials supported that early thrombectomy, as compared with alteplase alone, improved reperfusion, early neurologic recovery, and functional outcome.

There are several potential reasons that lead to these completely different results. First, the advances in device technology contribute to this shift. Earlier generation devices including coil retriever and aspiration devices failed to show clinical benefit in two phase 3 randomized clinical trials,

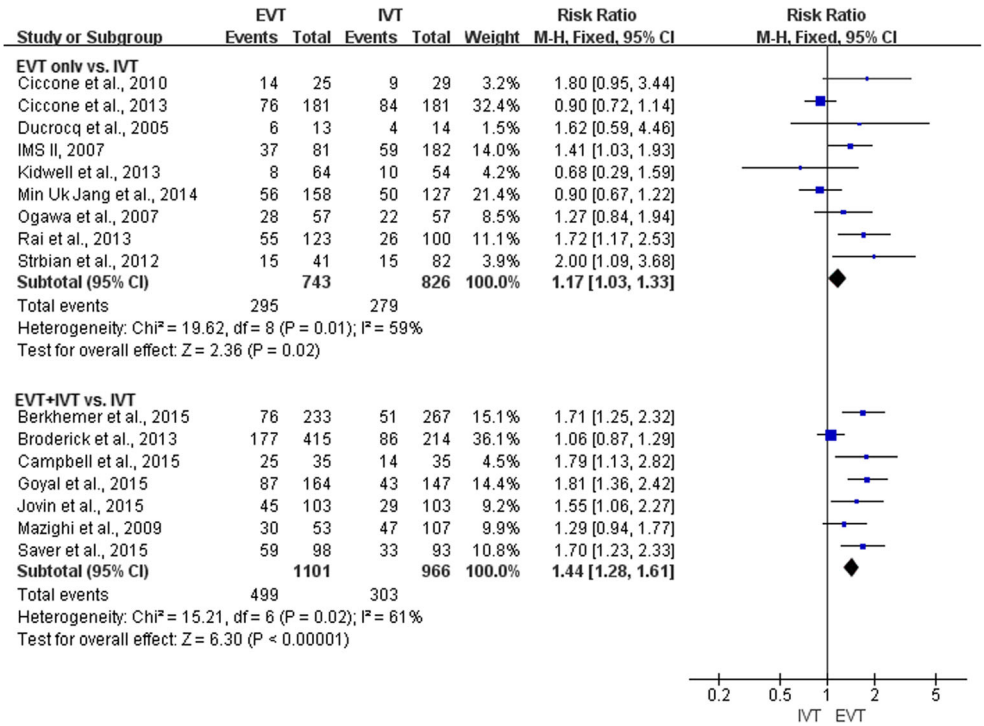

Fig. 3 Subgroup analysis of functional outcomes according to the type of endovascular treatment (EVT only or EVT plus IVT)

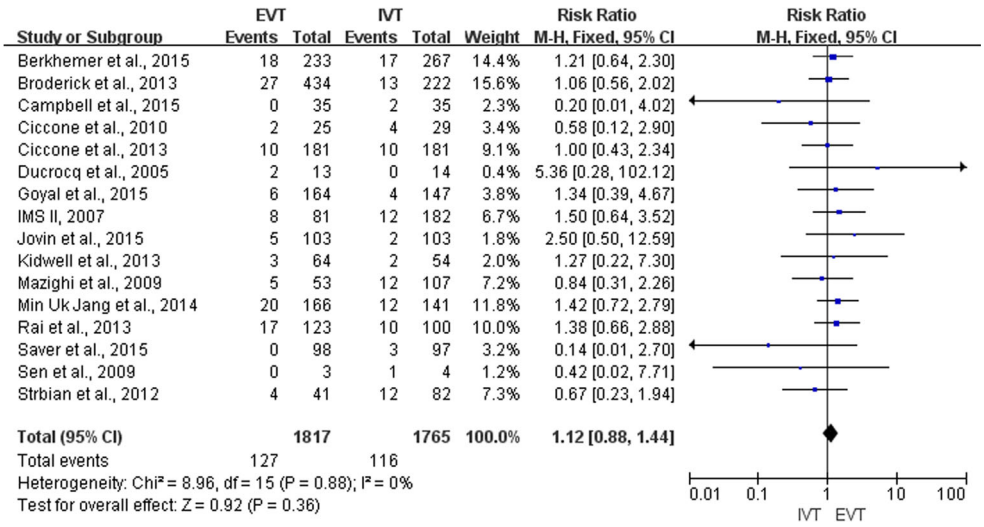

Fig. 4 Number of patients with symptomatic hemorrhagic transformation (SHT) for EVT compared with IVT

SYNTHESIS pilot trial and Interventional Management of Stroke, III (IMS III). On the other hand, the four recent randomized clinical trials of stent retrievers against medical treatment have established the benefits of EVT in patients [6, 12, 14, 28]. Moreover, improved recanalization, reduced mortality, and better functional outcomes with the stent retriever devices were observed when directly comparing the newer stent retriever devices with the earlier generation devices [33, 34]. Second, basic imaging selection was routinely done in recent trials to evaluate the location of the arterial occlusion and the extent of the penumbra, collateral blood flow status, and core infarct areas and thereby to improve patient selection for endovascular therapy. In particular, EXTEND-IA trial regarding perfusion imaging selection may be prudent to improve the science before changing clinical practice. Moreover, time from stroke onset to intervention is an important factor in the management of patients with AIS, with a decline in favorable outcomes with an increase in picture to puncture time. The ideal enrollment time needs to be taken into account in future trials of EVT compared with IVT. In addition, more adept skills as well as more standardized design of trials influence the results of the trials.

This is the first comprehensive systematic review and meta-analysis which takes into account all randomized controlled trials (RCTs) to assess the efficacy and safety of endovascular treatment in patients with acute ischemic stroke

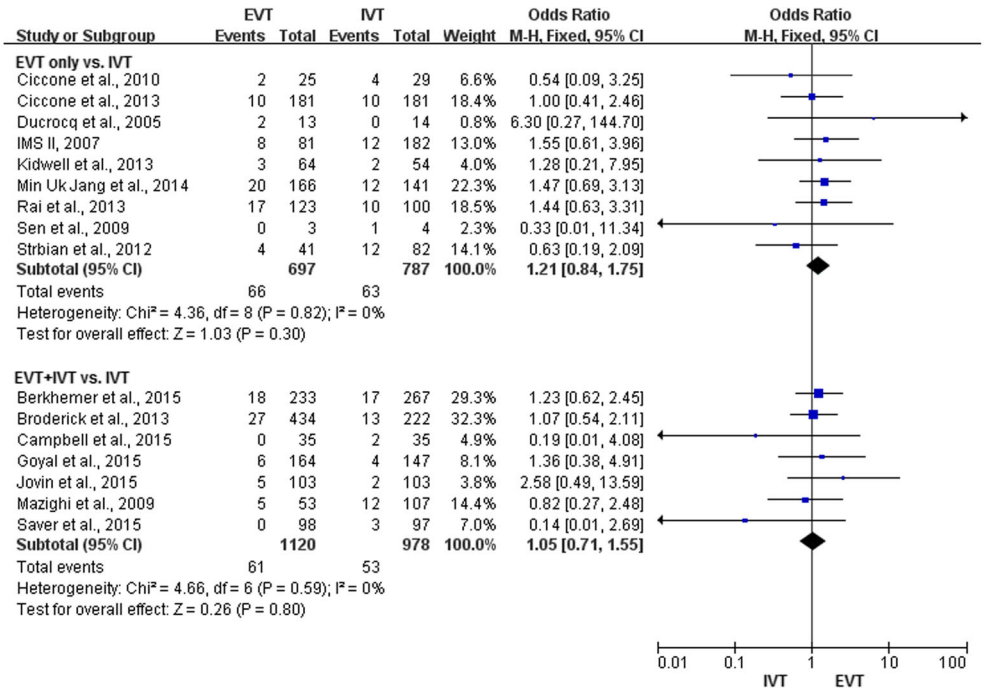

Fig. 5 Subgroup analysis of symptomatic hemorrhagic transformation (SHT) rate according to the type of endovascular treatment (EVT only or EVT plus IVT)

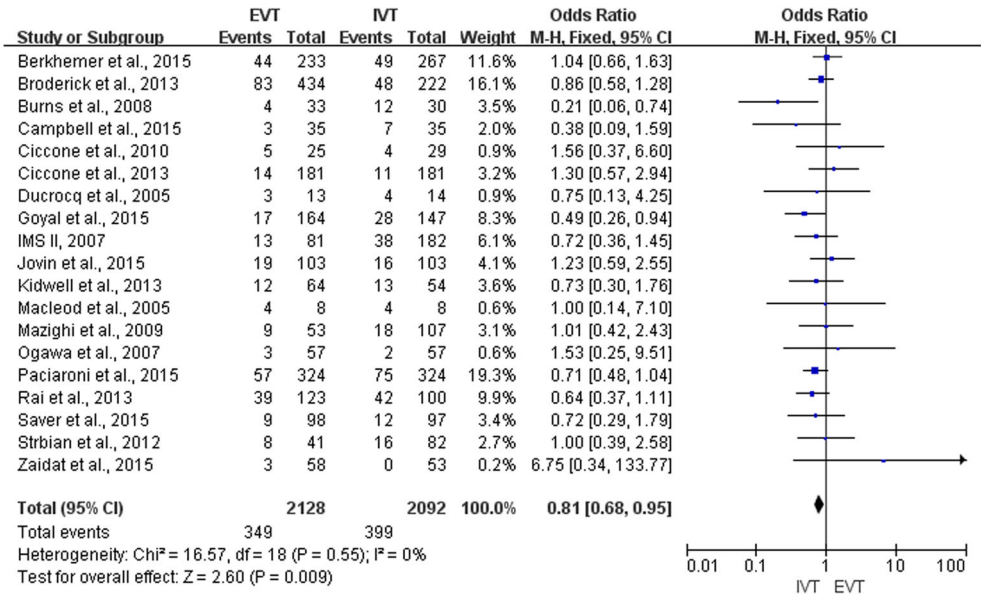

Fig. 6 Forest plot for analysis of mortality

as compared with intravenous thrombolysis. The results of this meta-analysis which provides evidence from 21 randomized controlled trials with 4473 participants can more powerfully estimate that rapid endovascular treatment is superior to intravenous thrombolysis for acute ischemic stroke (AIS). The strengths of our meta-analysis include a comprehensive search of all the major databases and manual search of the abstracts and proceedings of major conferences to avoid selection bias. We also did subgroup analyses providing similar results to the overall analysis, explaining the robustness of our study. Our study also has some limitations. One important concern is that the definition of "time to therapy" among the studies varies with the trials, which confused us and failed to analyze this key factor accurately. Similarly, lack of reported data about the location of the arterial occlusion lead to our failure in analyzing the effect of anterior versus posterior circulation stroke on patient outcome.

However, these limitations provide us with directions of acute ischemic stroke therapy trial design. The development of endovascular treatments has been challenging, with many

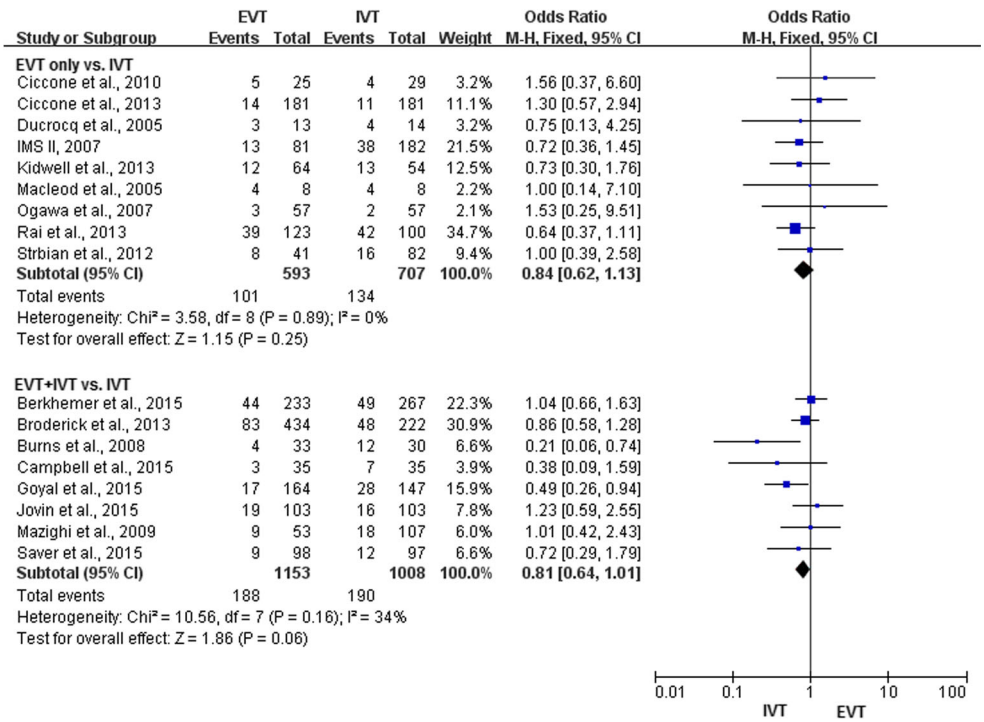

Fig. 7 Subgroup analysis of mortality according to the type of endovascular treatment (EVT only or EVT plus IVT)

disappointing trial outcomes and a few successes. A new era of endovascular treatment has arrived, and planning begins to extend the time window from within 6 h of stroke symptom onset to 6–12 h (POSITIVE) and 6–24 h (DAWN) with the use of perfusion imaging selection. Advanced imaging will play more and more important part in clinical trials and practice, which will analyze the effect of the arterial occlusion location on the efficacy of EVT. Simultaneously, several novel therapeutic targets including penumbral freezing, prevention of reperfusion injury, and enhanced recanalization efficacy should be directed in the following clinical trials.

Conclusions

Based on the current data, endovascular therapy may produce good clinical outcomes with similar symptomatic hemorrhage and mortality as compared with intravenous thrombolysis in acute ischemic stroke. With experience and dedication to reduce treatment delays, endovascular thrombectomy has the potential to achieve even greater benefits. This advancing intervention is a landmark change in stroke treatment and could be of huge potential benefit to patients worldwide.

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Author contributions LT and J-TY conceived the study. C-C T, H-FW, J-L J, and M-ST selected reports and extracted the data. C-C T and J-L J analyzed and interpreted the data. C-C T and J-TY wrote the first draft of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version. LT and J-TY are guarantors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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