Neuroradiology (2021) 63:17–25
https://doi.org/10.1007/s00234-020-02530-9

REVIEW

Safety and efficacy of tirofiban combined with endovascular therapy compared with endovascular therapy alone in acute ischemic stroke: a meta-analysis

Yingying Sun[1] · Zhen-Ni Guo[1] · Xiuli Yan[1] · Meiqi Wang[1] · Peng Zhang[1] · Haiqiang Qin[2] · Yan Wang[1] · Hongjing Zhu[1] · Yi Yang[1]

Received: 30 May 2020 / Accepted: 17 August 2020 / Published online: 25 August 2020

Abstract

Endovascular treatment (EVT) has been widely used for treating acute ischemic stroke (AIS). However, the safety and efficacy of treating AIS with tirofiban combined with EVT remain controversial. Therefore, we conducted a meta-analysis to evaluate this treatment. Randomized controlled trials and cohort studies that compared treatment with tirofiban combined with EVT and EVT alone were included in our meta-analysis. Those published from inception to March 31, 2020, were searched using the PubMed, Web of Science, Embase, and Cochrane Library databases. Safety was assessed based on symptomatic intracranial hemorrhage (sICH) incidence and 3-month mortality. Efficacy was assessed based on modified Rankin Scale (mRS) scores at 3 months post-EVT and recanalization rates. Data were analyzed using either the random-effects or fixed-effects model based on the heterogeneity of studies. In total, one RCT, six prospective studies, and four retrospective studies (2387 AIS cases) were assessed. Our meta-analysis showed that tirofiban combined with EVT did not increase sICH risk (RR, 1.06; 95%CI, 0.79 to 1.42; $P = 0.72$) and 3-month mortality (RR, 0.87; 95%CI, 0.74 to 1.04; $P = 0.12$). Recanalization rates were not significantly different between patients treated with tirofiban combined with EVT and those treated with EVT alone (RR, 1.04; 95%CI, 1.00 to 1.08; $P = 0.07$), but tirofiban combined with EVT was significantly associated with favorable functional outcomes (mRS score, 0–2) in AIS patients (RR, 1.13; 95%CI, 1.02 to 1.25; $P = 0.02$). Tirofiban combined with EVT appears to be safe and potentially effective in treating AIS.

Keywords Tirofiban · Acute ischemic stroke · Endovascular treatment · Meta-analysis

Introduction

Acute ischemic stroke (AIS) is one of the most common causes of disability and death worldwide [1]. Intravenous thrombolysis is considered the most effective therapy for AIS patients within 4.5 h, but endovascular treatment (EVT) may be superior in terms of achieving large artery revascularization, especially beyond the time window of intravenous thrombolysis [2]. However, EVT frequently leads to endothelial injuries, and the following platelet aggregation may cause thromboembolic complications and early reocclusion [3].

Tirofiban, a non-peptide platelet glycoprotein (GP) IIb/IIIa receptor inhibitor with a short half-life, can potently inhibit the final pathway of platelet activation and subsequent thrombus formation [4]. Currently, tirofiban has been widely used for AIS patients treated with EVT in order to improve clinical outcomes. However, there has been no consensus regarding the safety and efficacy of tirofiban in AIS patients treated with EVT. Therefore, we conducted a meta-analysis to evaluate the safety and efficacy of tirofiban combined with EVT in treating AIS patients by comparing it with EVT alone.

YS and Z-NG contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00234-020-02530-9) contains supplementary material, which is available to authorized users.

✉ Yi Yang
doctoryangyi@163.com; yang_yi@jlu.edu.cn

[1] Neuroscience Center & Clinical Trial and Research Center for Stroke, Department of Neurology, The First Hospital of Jilin University, Xinmin Street, Chang Chun, Jilin 130021, China

[2] Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Methods

Ethics

This meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis [5].

Search strategy

A systematic literature search was independently performed by two authors (Yingying Sun and Meiqi Wang) using the PubMed, Web of Science, Embase, and Cochrane Library databases. Literature published from inception to March 31, 2020, were searched. The following key words were used for finding relevant studies from the databases: "stroke," "cerebrovascular accident," "apoplexy," "brain vascular accident," "endovascular therapy," "endovascular procedures," "endovascular techniques," "thrombectomy," "recanalization," "tirofiban," "Aggrastat," "MK 383," and "L 700462," After identifying all potentially relevant articles, we removed duplicate articles with Endnote X9 reference management software. The two authors independently assessed the title, abstract, and full text of each article identified by the literature search for inclusion. Moreover, we reviewed the reference lists of the retrieved articles to identify any omitted studies.

Study selection

The inclusion criteria for articles were as follows: (1) studies that compared patients with AIS who were treated with EVT combined with tirofiban to those treated with EVT alone; (2) randomized controlled trials (RCTs) and cohort studies; (3) studies that reported on at least one of the following outcomes: symptomatic intracranial hemorrhage (sICH), mortality, modified Rankin Scale (mRS) score at 3 months post-EVT, and recanalization rate; and (4) studies published in English. The exclusion criteria were as follows: (1) duplicated articles and studies with populations that came from duplicate databases; (2) single-arm trials, editorials, letters to the editor, conference abstracts and posters, review articles, case reports, and animal experimental studies; and (3) articles in which relevant data could not be extracted.

Outcomes

The safety outcomes we assessed were sICH incidence and mortality at 3 months post-EVT. sICH was defined according to the European Cooperative Acute Stroke Study III definition [6]. The efficacy outcomes we assessed were mRS score at 3 months post-EVT and recanalization rate. mRS scores ranged from 0 (no symptoms) to 6 (death) [7]. A favorable functional outcome was defined as an mRS score of 0–2. Recanalization was defined as a Tissue Thrombolysis in Cerebral Ischemia (TICI) score of ≥ 2b, as determined via angiogram scans or magnetic resonance imaging.

Data extraction and quality assessment

Data from studies were independently extracted and assessed by two authors (Yingying Sun and Meiqi Wang) in accordance with the inclusion criteria mentioned above. Disagreements were solved by consensus. The following information was extracted from eligible studies: name of the first author, year of publication, study country, study design, study center, sample size, occlusion location, therapeutic strategies, rate of bridging therapy, and general information on the use of tirofiban. The quality of cohort studies was assessed with the Newcastle-Ottawa Scale (NOS) [8]. NOS scores ranged from 0 to 9 and were assessed based on the following three factors: selection, comparability, and outcome. Cohort studies with an NOS score of ≥ 7 and RCTs were considered high in quality.

Statistical analysis

All meta-analyses were performed using Review Manager for Windows version 5.2 and STATA 12.0. Risk ratios (RRs) were calculated for dichotomous variables, and all results are reported with 95% confidence intervals (95%CIs). We assessed statistical heterogeneity between studies using chi-square tests, with a P value of < 0.1 considered statistically significant. Heterogeneity was quantified using I^2 values; an I^2 value of ≥ 50% indicated heterogeneity [9]. If heterogeneity among studies was detected, we used the random-effects model for meta-analyses. If not, we used the fixed-effects model. Data were presented as forest plots, with a P value of < 0.05 considered statistically significant. A sensitivity analysis was conducted through leave-one-out cross validation to assess the stability of meta-analysis results. Publication bias was assessed by funnel plot symmetry [10].

Results

Search results and study characteristics

The initial literature search yielded a total of 898 studies. After assessing these studies, 11 studies, which included 2387 AIS cases, met the inclusion criteria and were included in the final analysis. The literature search and screening process are described in Fig. 1. Our meta-analysis included one RCT [11], six prospective cohort studies [12–17], and four retrospective cohort studies [18–21]. Study characteristics and quality assessment results are shown in Table 1. General information on

Table 1 Study characteristics and methodological quality assessment results

Author (year)	Country	Study design	Study center	Sample size	Occlusion location	Therapeutic strategies	Bridging therapy, *n* (%)	Newcastle-Ottawa Quality Assessment Scale		
								Selection	Comparability	Outcome
Kellert et al. (2013) [12]	Germany	Prospective cohort	Single-center	162	Anterior + posterior	MT/stenting	114 (70.4)	★★★★	★★	★★★
Zhao et al. (2017) [13]	China	Prospective cohort	Single-center	180	Anterior + posterior	MT/stenting /balloon angioplasty	42 (23.3)	★★★★	★★	★★★
Yu et al. (2018) [18]	China	Retrospective cohort	Single-center	54	Anterior + posterior	MT	16 (29.6)	★★★☆	★★	★★★
Wu et al. (2018) [14]	China	Prospective cohort	Multiple-center	218	Anterior + posterior	MT/stenting /balloon angioplasty	48 (22.0)	★★★★	★☆	★★★
Pan et al. (2019) [15]	China	Prospective cohort	Single-center	211	Anterior + posterior	MT/stenting /balloon angioplasty	0 (0)	★★★★	★★	★★★
Zhang et al. (2019) [11]	China	Prospective study	Single-center	120	Anterior + posterior	MT/stenting/ balloon dilation	36 (30.0)	RCT		
Sun et al. (2019) [16]	China	Prospective cohort	Multiple-center	195	Anterior + posterior	MT/stenting /balloon angioplasty	79 (40.5)	★★★★	★★	★★★
Quan et al. (2019) [19]	China	Retrospective cohort	Multiple-center	159	Posterior	MT/stenting /balloon angioplasty	33 (20.8)	★★★☆	★★	★★★
Yi et al. (2019) [20]	Korea	Retrospective cohort	Multiple-center	327	Anterior + posterior	MT	133 (40.7)	★★★☆	★★	★★★
Luo et al. (2019) [21]	China	Retrospective cohort	Single-center	99	Anterior + posterior	MT/stenting /angioplasty	NR	★★★☆	★★	★★★
Yang et al. (2020) [17]	China	Prospective cohort	Multiple-center	662	Anterior + posterior	MT/stenting /balloon angioplasty	207 (31.1)	★★★★	★★	★★★

MT, mechanical thrombectomy; *NR*, not reported; *RCT*, randomized controlled trial

the use of tirofiban is shown in Table 2. All included studies were considered high in quality.

Safety and efficacy outcomes

sICH incidence

Of the 2387 AIS patients, 2382 from the 11 studies were included in the safety analysis regarding sICH incidence (5 patients lost to follow-up in the original studies). There was no significant difference in the incidence of sICH between patients treated with tirofiban combined with EVT and those treated with EVT alone (RR, 1.06; 95%CI, 0.79 to 1.42; P = 0.72) (Fig. 2). There was no significant heterogeneity between these studies (I^2 = 21%, P = 0.24).

3-month mortality

All 2387 patients were included in the safety analysis regarding mortality at 3 months post-EVT. There was no significant difference in the rates of mortality between patients treated with tirofiban combined with EVT and those treated with EVT alone (RR, 0.87; 95%CI, 0.74 to 1.04; P = 0.12) (Fig. 3). There was no significant heterogeneity between these studies (I^2 = 0%, P = 0.53).

Favorable functional outcomes

In total, 10 studies reported that 2161 patients exhibited favorable functional outcomes at 3 months post-EVT. The meta-analysis showed that tirofiban combined with EVT was

Table 2 General information on the use of tirofiban

Author (year)	Dosage	Route of administration	Indications
Kellert et al. (2013) [12]	NR (adapted for weight and administered for at least 12 h)	IV	Patients who were treated with stenting or at high risk of relevant endothelial damage
Zhao et al. (2017) [13]	IA: 0.25–0.5 mg or IV: 0.2–0.25 mg/h × 12–24 h	IA/IV	Based on occlusion characteristics and relevant procedures
Yu et al. (2018) [18]	0.2–0.5 mg	IA	Patients who presented with distal vessel occlusion
Wu et al. (2018) [14]	3.4 μg/kg or 6.7 μg/kg or 10 μg/kg	IA	Patients who underwent endovascular thrombectomy
Pan et al. (2019) [15]	0.15 μg/kg/min × 16–24 h	IV	Patients who were at high risk of early reocclusion
Zhang et al. (2019) [11]	0.2 μg/kg/min or 0.1 μg/kg/min	IA	Based on the random number table method
Sun et al. (2019) [16]	0.25–0.5 mg	IA	(1) The target artery remained occluded after thrombectomy; (2) reocclusion of the recanalized artery; (3) residual stenosis ≥ 50% in occlusion site after thrombectomy; (4) multiple attempts with retriever during thrombectomy (≥ 3 times)
Quan et al. (2019) [19]	IA: 0.25–0.5 mg or IV: 0.2–0.25 mg/h × 12–24 h	IA/IV	Patients who were treated with primary or rescue balloon angioplasty (without or with stenting)
Yi et al. (2019) [20]	0.25–1.0 mg at 0.05 mg/min (max ≤ 1.0 mg)	IA	(1) Micro-catheter or micro-wire failed to pass the occluded segment; (2) no response to first stent retrieval; (3) reocclusion of partially recanalized vessel after stent retrieval
Luo et al. (2019) [21]	50 μg/kg at 50 μg/min	IV	After appropriate imaging confirming the presence of a proximal vessel occlusion and distinct ischemic penumbra
Yang et al. (2020) [17]	IA: 0.25–1 mg + IV: 0.1 μg/kg/min × 24 h	IA + IV	According to intraoperative status of artery recanalization

IV, intravenous; *IA*, intra-arterial; *NR*, not reported

significantly associated with favorable functional outcomes (RR, 1.13; 95%CI, 1.02 to 1.25; $P = 0.02$) (Fig. 4). There was no significant heterogeneity between these studies ($I^2 = 13\%$; $P = 0.32$).

Recanalization rate

In total, nine studies reported that 2031 patients exhibited recanalization after EVT. There was no significant difference in recanalization rates between patients treated with tirofiban combined with EVT and those treated with EVT alone (RR, 1.04; 95%CI, 1.00 to 1.08; $P = 0.07$) (Fig. 5). There was no significant heterogeneity between these studies ($I^2 = 34\%$; $P = 0.14$).

Sensitivity analysis and publication bias

The results of the sensitivity analysis are shown in Supply 1-4. The sensitivity analysis showed that after removing the study reported by Wu et al. [14], patients treated with tirofiban and EVT had a lower rate of mortality at 3 months post-EVT than those treated with EVT alone (Supply 2). Furthermore, after removing the studies reported by Pan et al. [15] and Sun et al. [16], the sensitivity analysis showed that there was no significant difference in terms of the incidence of favorable functional outcomes at 3 months post-EVT between patients treated with tirofiban and EVT and those treated with EVT alone (Supply 3). Then, after removing the study reported by Zhao et al. [13], the sensitivity analysis showed that patients treated with tirofiban and EVT had higher recanalization rates than those treated with EVT alone (Supply 4). The other sensitivity analysis results were consistent with those of the primary analysis.

With regard to the funnel plot analysis, the shape of the funnel plot did not indicate obvious asymmetry upon visual inspection (Supply 5-8).

Discussion

Ours is the first meta-analysis to evaluate the safety and efficacy of tirofiban combined with EVT in treating patients with AIS. We found that tirofiban combined with EVT did not increase the risk of sICH and 3-month mortality. Moreover, there was no significant difference in recanalization rates between patients treated with tirofiban combined with EVT and those treated with EVT alone. However, tirofiban combined

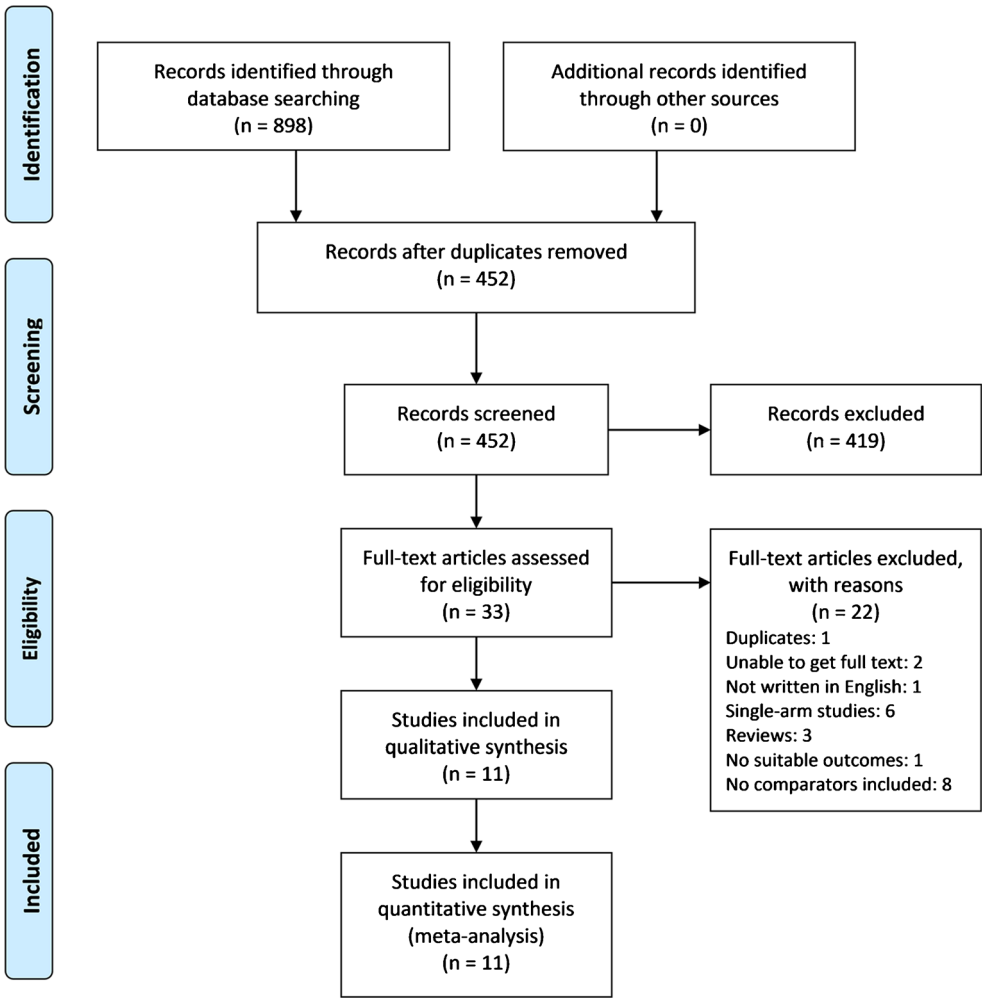

Fig. 1 A flow chart depicting how studies were searched and screened

with EVT was more likely to achieve favorable functional outcomes.

The safety and efficacy of treating AIS with tirofiban therapy remain controversial. In a previous meta-analysis, researchers suggested that treating AIS with tirofiban did not increase the risk of sICH and mortality and did not provide any obvious improvements in terms of functional outcomes [22]. Simultaneously, the study by Zhou et al. [23] found that,

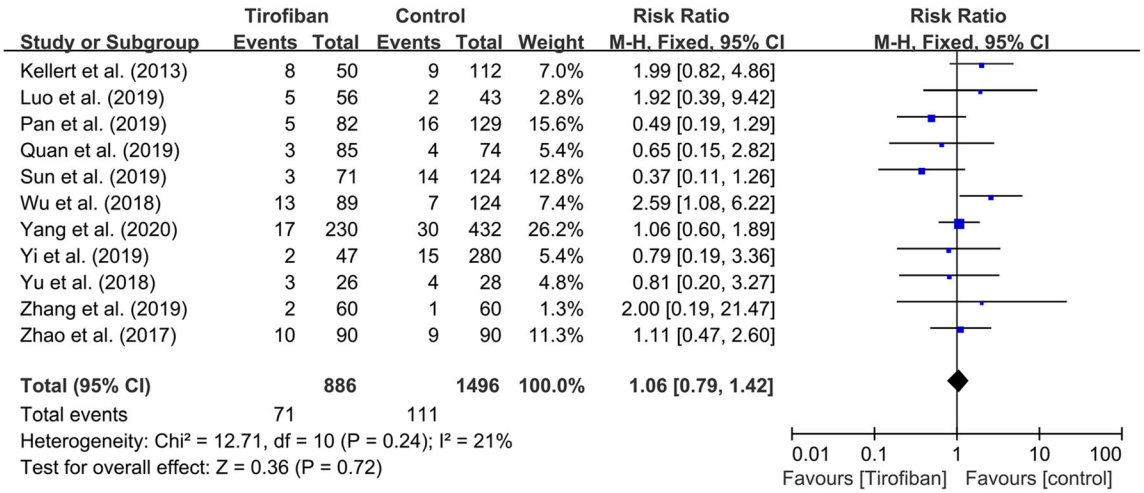

Fig. 2 A forest plot for assessing the incidence of symptomatic intracranial hemorrhage in acute ischemic stroke patients who underwent endovascular therapy

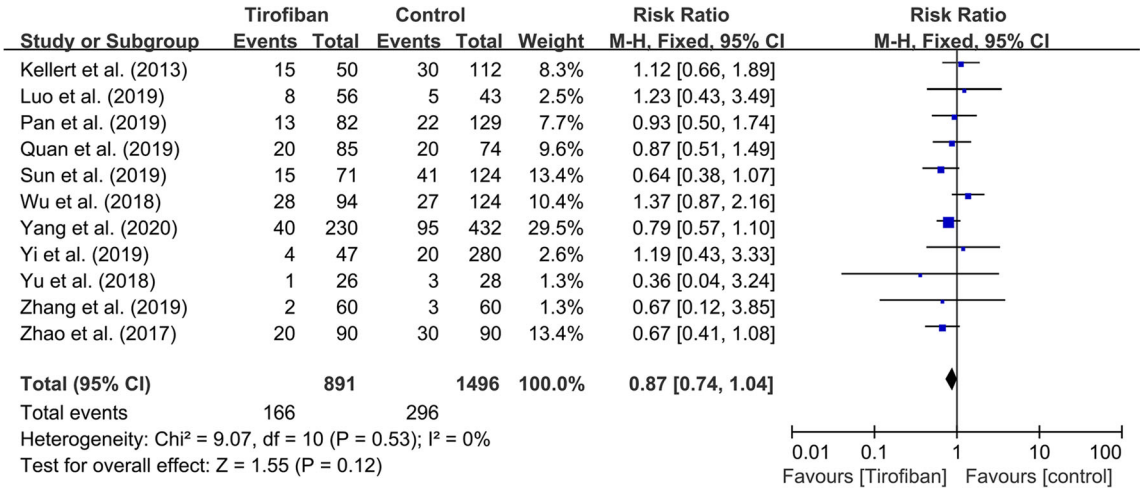

Fig. 3 A forest plot for assessing 3-month mortality in acute ischemic stroke patients who underwent endovascular therapy

for patients with AIS who underwent intravenous thrombolysis, tirofiban therapy may be safe, but its role in improving functional outcomes was unclear. Compared with previous studies, our meta-analysis included more recently published studies relatively and we further found that tirofiban combined with EVT increased the incidence of favorable functional outcomes and did not increase the risk of sICH and mortality in treating AIS patients. Additionally, while our meta-analysis demonstrates that tirofiban combined with EVT can be safe and effective in treating AIS patients, several studies included in our meta-analysis have indicated the opposite. For instance, Kellert et al. [12] showed a higher risk of fatal ICH and poor outcome in patients treating tirofiban combined with EVT. The following reasons may have attributed to this discrepancy. On the one hand, this study [12] was published in 2013, while the other studies included in our meta-analysis were published after 2015. Therefore, it should be noted that the clinical guidelines regarding the indication for EVT for AIS patients were updated in 2015 [24]. On the other hand, this study was the only non-Chinese study. It is known that the etiology and pathology of AIS in Chinese population is different from that in Western population. Furthermore, a study by Wu et al. [14] showed that tirofiban was associated with an increased risk of bleeding during EVT in AIS patients. However, after removing this study [14] from our sensitivity analysis, it showed that patients treated with tirofiban and EVT had lower mortality rates than those treated with EVT alone. This may be due to the fact that, unlike the other included studies, this study [14] focused on the relationship between different doses of tirofiban and the risk of bleeding during EVT and mortality. Different doses of tirofiban may result in different outcomes. Fortunately, the sensitivity analysis for our other outcomes showed that these two studies did not change the final result, thereby indicating the stability of our results.

Furthermore, the rate of recanalization after EVT is one of the main predictors for functional outcomes in AIS patients. Microvascular thrombosis may remain in situ after blood vessel occlusions are recanalized via EVT [25]. Several studies have reported that tirofiban can prevent platelet aggregation,

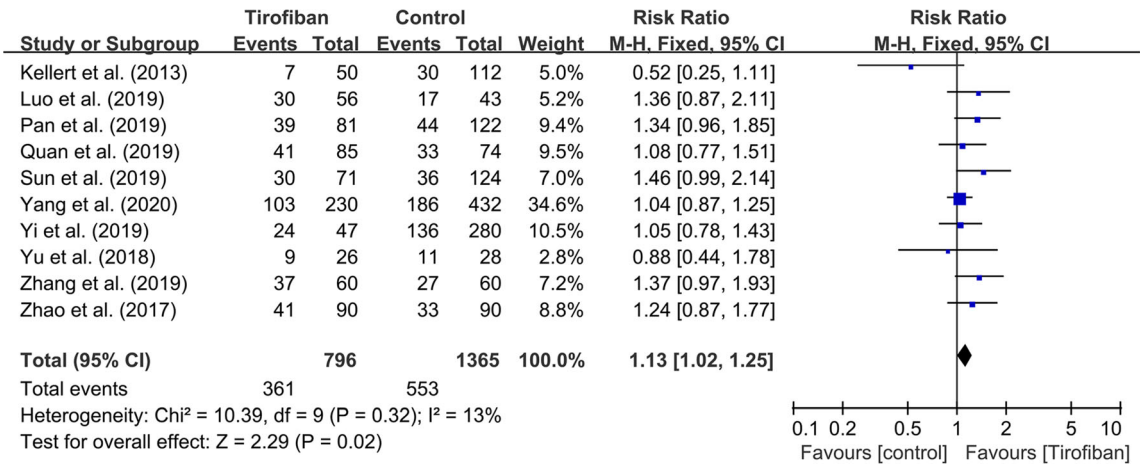

Fig. 4 A forest plot for assessing the incidence of favorable functional outcomes in acute ischemic stroke patients who underwent endovascular therapy

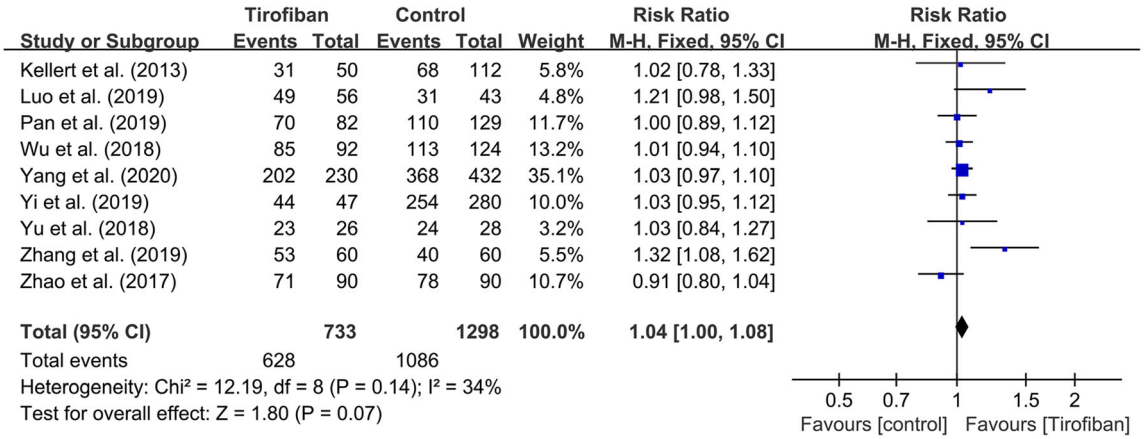

Fig. 5 A forest plot for assessing recanalization rates in acute ischemic stroke patients who underwent endovascular therapy

thereby inhibiting microthrombus formation and improving the level of tissue reperfusion [25, 26]. After removing Zhao et al.'s [13] study from our sensitivity analysis, it showed that patients treated with tirofiban and EVT had higher recanalization rates and lower 3-month mRS scores than those treated with EVT alone. Zhao et al.'s [13] study demonstrated that interventionists were prone to use tirofiban in patients with a high risk of reocclusion after arterial occlusions were recanalized. This selection bias may have undervalued the rate of recanalization in patients treated with tirofiban and EVT. Therefore, we speculate that tirofiban is effective in treating AIS patients who undergo EVT. More randomized controlled trials are needed to further evaluate whether tirofiban can improve post-EVT recanalization rates.

Additionally, sICH is a major complication of EVT for AIS patients. The main reason that sICH occurs after EVT may be due to the combination of antiplatelet therapy [27]. However, our meta-analysis showed that tirofiban combined with EVT did not increase the risk of sICH and mortality. This may be attributed to the possible advantages that tirofiban has over other antiplatelet drugs. Tirofiban is a fast-acting and fast-deactivated GP IIb/IIIa antagonist that is rapidly eliminated after infusion cessation due to its short half-life (about 2 h) [4]. Moreover, tirofiban can selectively inhibit fibrinogen from binding to platelets and prevent subsequent platelet aggregation, which makes platelet function reversible after infusion cessation [28]. Therefore, the incidence of bleeding caused by tirofiban is lower than other antiplatelet drugs, meaning that tirofiban therapy may be safe when combined with EVT.

This study has several limitations. Firstly, our meta-analysis included only one RCT, while the other studies were cohort studies. This may increase the risk of bias because of insufficient random sequence generation and blinding. Secondly, the included studies reported several different EVT strategies, including mechanical thrombectomy, stenting, and balloon angioplasty. Furthermore, these studies had different occlusion locations, rates of bridging therapy, and the information on the use of tirofiban. These differences may have influenced our final outcomes. Lastly, our sensitivity analysis showed that the incidence rates of favorable functional outcomes in our meta-analysis were not stable. Thus, more RCTs are needed to fully elucidate the efficacy of tirofiban combined with EVT in treating AIS patients.

In conclusion, we found that tirofiban therapy significantly increased the incidence of favorable functional outcomes and did not increase the risk of sICH and mortality in the Chinese population. Considering that there was only one RCT and one non-Chinese study among the 11 included studies, more RCTs and non-Chinese studies are needed to evaluate the efficacy and safety of tirofiban combined with EVT in the future.

Acknowledgments We would like to thank Editage (www.editage.cn) for English language editing.

Funding information This study was funded by the National Key R&D Program of China (2016YFC1301600), JLUSTIRT (2017TD-12), and Science and Technology Department of Jilin Province (20180623052TC) to Yi Yang.

Data availability Not applicable.

Compliance with ethical standards

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

Ethical approval Ethical approval for this study was not required because this manuscript did not contain patient data and we only performed data analysis based on published studies.

Informed consent Informed consent was not required because this manuscript did not contain patient data and it is a meta-analysis based on published studies.

Consent to participate Not applicable.

Consent to publication Not applicable.

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