Heliyon 9 (2023) e15842

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Efficacy and safety of intracoronary versus intravenous tirofiban in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
ST-elevation myocardial infarction
Percutaneous coronary intervention
Tirofiban
Meta-analysis
Randomized controlled trial

ABSTRACT

Background: Effective antiplatelet therapy is critical for patients with ST-segment elevation myocardial infarction (STEMI) and receiving primary percutaneous coronary interventions (PPCI). Intracoronary (IC) and intravenous (IV) administration of tirofiban are commonly used during the procedure of PPCI. However, which is the better administration route of tirofiban have not been fully evaluated.

Methods: A comprehensive literature search of RCTs that comparing IC with IV tirofiban in STEMI patients undergoing PPCI was conducted, which were published as of May 7, 2022, in PubMed, Embase, Cochrane Library, Web of Science, Scopus and ClinicalTrials.gov. The primary efficacy endpoint was 30-day major adverse cardiovascular events (MACE) and the primary safety endpoint was in-hospital bleeding events.

Results: This meta-analysis included 9 trials involving 1177 patients. IC tirofiban significantly reduced the incidence of 30-day MACE (RR 0.65, 95% CI: 0.44 to 0.95, P = 0.028) and improved the rate of the thrombolysis in myocardial infarction (TIMI) grade 3 flow in high-dose (25 μg/kg) group (RR = 1.13, 95% CI: 0.99–1.30, P = 0.001), in-hospital (WMD 2.03, 95% CI: 1.03 to 3.02, P < 0.001), and 6-month left ventricular injection fraction (LVEF) (WMD 6.01, 95% CI: 5.02 to 6.99, P < 0.001) compared with IV. There was no significant difference in the incidences of in-hospital bleeding events (RR 0.96, 95% CI: 0.67 to 1.38, P = 0.82) and thrombocytopenia (RR 0.63, 95% CI: 0.26 to 1.57, P = 0.32) between the two groups.

Conclusions: IC tirofiban significantly improved the incidence of TIMI 3 in the high-dose group, in-hospital and 6-month LVEF, and reduced the 30-day MACE incidence without increasing the risk of bleeding compared with IV.

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https://doi.org/10.1016/j.heliyon.2023.e15842
Received 13 December 2022; Received in revised form 22 April 2023; Accepted 24 April 2023
Available online 28 April 2023

1. Introduction

ST-segment elevation myocardial infarction (STEMI) is a severe type of acute coronary syndrome (ACS), accompanied by the activation of platelets and coagulation systems [1]. Timely symptomatic relief and prevention of complications are particularly important for the treatment of STEMI patients, primary percutaneous coronary intervention (PPCI) is currently the main method of early reperfusion therapy which can improve the prognosis of STEMI patients. Meanwhile, effective antiplatelet therapy is essential for these patients [2]. Glycoprotein IIb/IIIa inhibitors (GPIs) including tirofiban, abciximab and eptifibatide are supposed to be the most effective inhibitors of platelet aggregation [3].

Tirofiban is a small molecule non-peptide cyclin reversible antagonist of the platelet GPIIb/IIIa receptor. After discontinuation of tirofiban, platelet function can recover more than a half in 2 h [4]. As one of the GPIs, tirofiban prevents the binding of fibrinogen and von Willebrand factor (vWF) to platelet glycoprotein (GP) IIb/IIIa receptors and then hinders platelet aggregation to prevent stent thrombosis [5]. And tirofiban has been proven to reduce infarct area and improve ST-resolution without increasing the incidence of bleeding events and major adverse cardiac and cerebrovascular events (MACCE) in STEMI patients [6]. Unlike tirofiban, abciximab is a monoclonal antibody with a strong binding ability to GP IIb/IIIa receptor, which is prone to bleeding complications because platelet aggregation function cannot return to normal for a long time after discontinuation of the drug. Moreover, abciximab will increase the mortality rate of patients [7,8]. Intracoronary administration confers more benefit than intravenous abciximab, but it is controversial whether tirofiban has the same efficacy as abciximab [9]. Although tirofiban was less protective against major ischemic events than abciximab, there was no difference in the incidence of major adverse cardiovascular events (MACE) between tirofiban and abciximab [10]. Additionally, tirofiban had a lower incidence of minor bleeding events and thrombocytopenia, and the cost was much lower than the latter. Therefore, tirofiban might be a better choice for these STEMI patients undergoing PPCI [11].

The 2021 guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) recommends selective intravenous (IV) GPIs in STEMI patients [12]. However, the efficacy and safety of intracoronary (IC) GPIs after a guidewire or balloon passing through the infarction-associated arteries (IRA) is not mentioned. Some studies showed that IC GPIs significantly improve microvascular perfusion and subsequent clinical outcomes compared with IV, while others found no additional benefit of IC GPIs in the perioperative period [13–15]. Whether IC GPIs would be better compared to IV remained controversial. Therefore, we conducted a meta-analysis of all currently available randomized controlled trials (RCTs) to investigate the efficacy and safety of IC versus IV injection of tirofiban in STEMI patients undergoing PPCI treatment.

2. Methods

We conducted this meta-analysis through a pre-established research protocol and adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during this process [16]. This meta-analysis was registered with PROSPERO number CRD42022328891.

2.1. Search strategy

The searched Medical Subject Headings (MeSH) mainly included ST Elevation Myocardial Infarction, Percutaneous Coronary Intervention, Tirofiban, and Randomized Controlled Trial. Other searched terms included Intracoronary and these free words that were searched from entry terms part of each MeSH in PubMed. Two authors (Rui Tian and Rugang Liu) independently conducted a comprehensive search of the databases including PubMed, Embase, Cochrane Library, Web of Science and Scopus. The RCTs searched were limited to publication before May 7, 2022 and the language was limited to English or Chinese. In addition, we manually searched clinicaltrials.gov for potential RCTs that had not been published, but we did not find any RCTs that conformed to the eligibility criteria. Simultaneously, we reviewed the relevant meta-analyses and literature to ensure that all relevant RCTs were contained in our study.

2.2. Study selection

The inclusion criteria for our study were as follows: ①randomized-controlled design; ②English or Chinese language; ③Consecutive enrollment of STEMI patients undergoing PPCI; ④The article contained the comparison of IC and IV tirofiban; ⑤At least one primary outcome to determine the efficacy or safety of tirofiban was reported.

2.3. Data extraction

Two investigators (Rui Tian and Rugang Liu) independently reviewed published papers and screened abstract and full-text versions of all studies that conformed to the inclusion criteria, and then independently recorded data by using predesigned forms. The following information was collected: ①Publication details (such as the first author's family name, year of publication, period of study, and study design); ②Trial information (such as study design, inclusion and exclusion criteria, sample size, intervention, and follow-up); ③Patient characteristics (such as age, gender, dual-antiplatelet therapy, cardiovascular risk factors, target vessel of coronary artery disease, and the PPCI related information); ④Outcome measures {such as MACE, bleeding events, thrombolysis in myocardial infarction (TIMI) grade 3 flow, left ventricular ejection fraction (LVEF), and thrombocytopenia}. Any divergence was resolved through a third author (Xiaoxing Li).

2.4. Quality assessment

The quality of the studies was assessed by two authors (Jiajun Zhang and Yong Li) following the Cochrane Collaboration. We evaluated the risk of analytical, selection, detection, reporting, and attrition bias for each RCT. Discrepancies were resolved by consultation with the third author (Xiaoxing Li).

2.5. Clinical outcomes

We extracted the following clinical outcomes from each included RCT: ①MACE; ②In-hospital bleeding events; ③TIMI grade 3 flow; ④LVEF; ⑤Thrombocytopenia (Supplementary Table 1). The primary efficacy outcome was 30-day MACE. Secondary efficacy outcomes were the TIMI grade 3 flow after stenting and LVEF. The primary safety outcome was in-hospital bleeding events and the secondary safety outcome was thrombocytopenia.

2.6. Statistical analysis

This study was implemented by using the Cochrane risk bias assessment tool Review Manager 5.4 software to assess the risk of bias of the included RCTs, the StataMP 17.0 statistical software to complete the data collection and perform a meta-analysis, and the GraphPad Prism 9 software to generate graphs. The effect size of count and measurement data was pooled as risk ratio (RR) and weighted mean difference (WMD), respectively with a 95% confidence interval (CI). Heterogeneity was assessed by Higgins and Thompson's I^2 statistic, with values of <25%, 26%–50%, 51%–75%, and >75% corresponding to insignificant, low, moderate, and high levels of heterogeneity [17]. If the results of each study showed that $I^2 \leq 50\%$ and $P > 0.1$, indicating that the heterogeneity between studies was not statistically significant, the Mantel-Haenszel fixed effects model was selected for meta-analysis; ②If the results of each study showed that $50\% < I^2 \leq 75\%$ and $P \leq 0.1$, the DerSimonian-Laird random effects model was selected for meta-analysis;

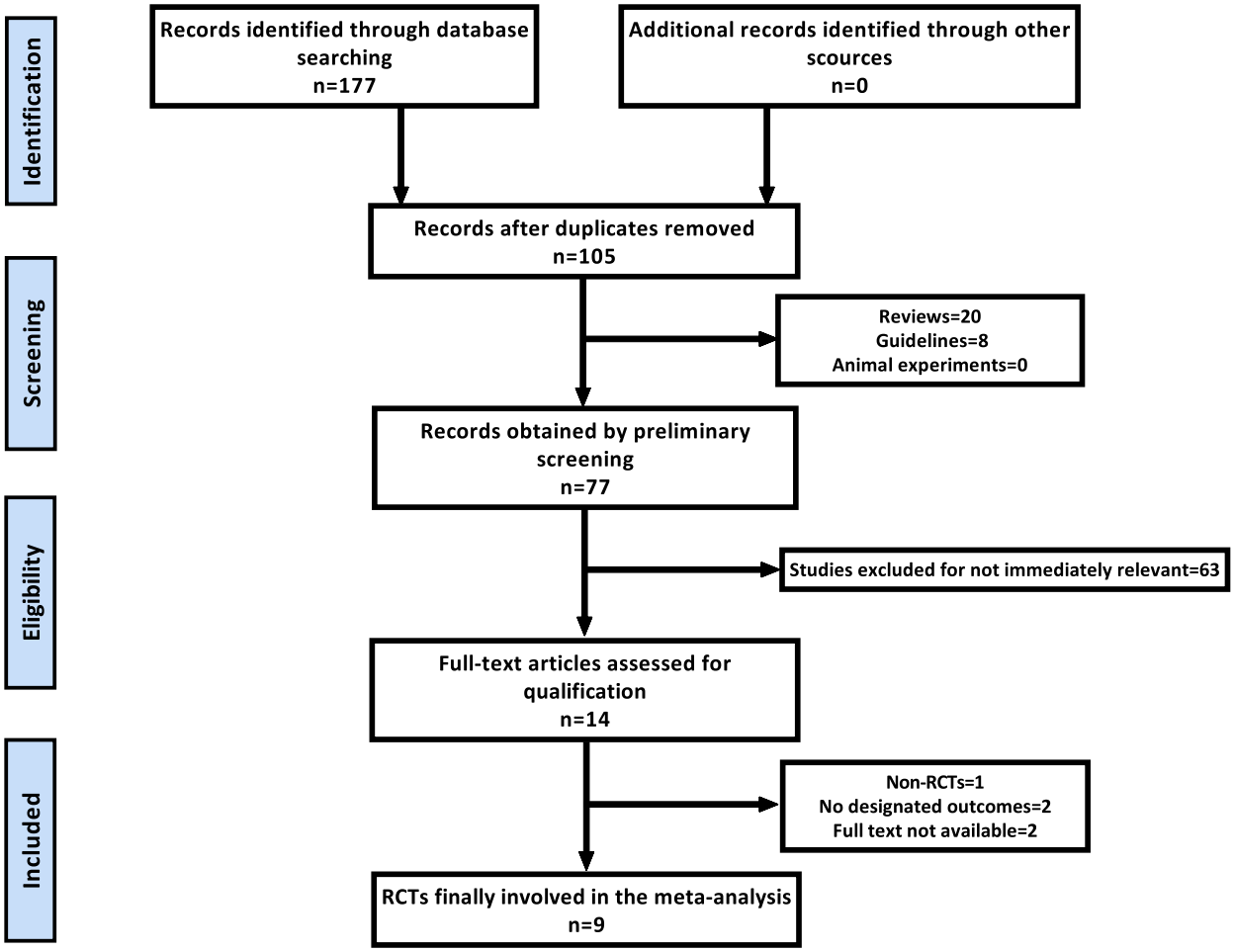

Fig. 1. Risk of bias summary and graph in the included literature. (A). Risk of bias summary. (B). Risk of bias graph.

③If the results of each study show that 75% < I^2 and P ≤ 0.1, sensitivity analysis, subgroup analysis, meta-regression, and other methods could be used to explore the source of heterogeneity; ④If the results of each study showed I^2 > 90% and P ≤ 0.1, meta-analysis was not performed. Sensitivity analysis was performed by using the exclusion method. A 2-tailed P < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Search results and risk of bias

We identified 177 potentially relevant articles through our search strategy, but not found additional records identified through other sources. After excluding duplicate research and screening the titles and abstracts of these potential articles, we reviewed 14 potentially relevant articles in full. After a comprehensive evaluation, 9 RCTs were involved in the analysis [15,18–25] (Fig. 1). The risk of bias 1.0 (RoB 1.0) assessment was described in the risk of bias table for each included trial. (Fig. 2A and B).

3.2. Study characteristics

As shown in Table 1, the studies involved 1177 patients, of whom 597 were randomized to the group of intracoronary tirofiban and 580 to the group of intravenous tirofiban, and the main baseline characteristics of these articles were detailed in Table 2 and Table 3. The ADP receptor inhibitors aspirin (300 mg) and clopidogrel (300 mg or 600 mg) were administered preoperatively in all included studies. Preoperative heparin use (50–100 IU/kg) was recorded except for the study of Zhou et al., Li et al., and Zhang et al. General information included that the male was 75.2% vs. 73.6% (P = 0.50), the mean age was 62.0 ± 11.5 vs. 61.3 ± 11.9 (P = 0.14), the prevalence of patients with Killip class II-IV and 3-vessel disease was 16.5% vs. 17.0% (P = 0.83), and 25.1% vs. 23.8% (P = 0.78), respectively. In the risk factors of cardiovascular diseases, the proportions of hypertension, diabetes mellitus, and smoking were 82.0%

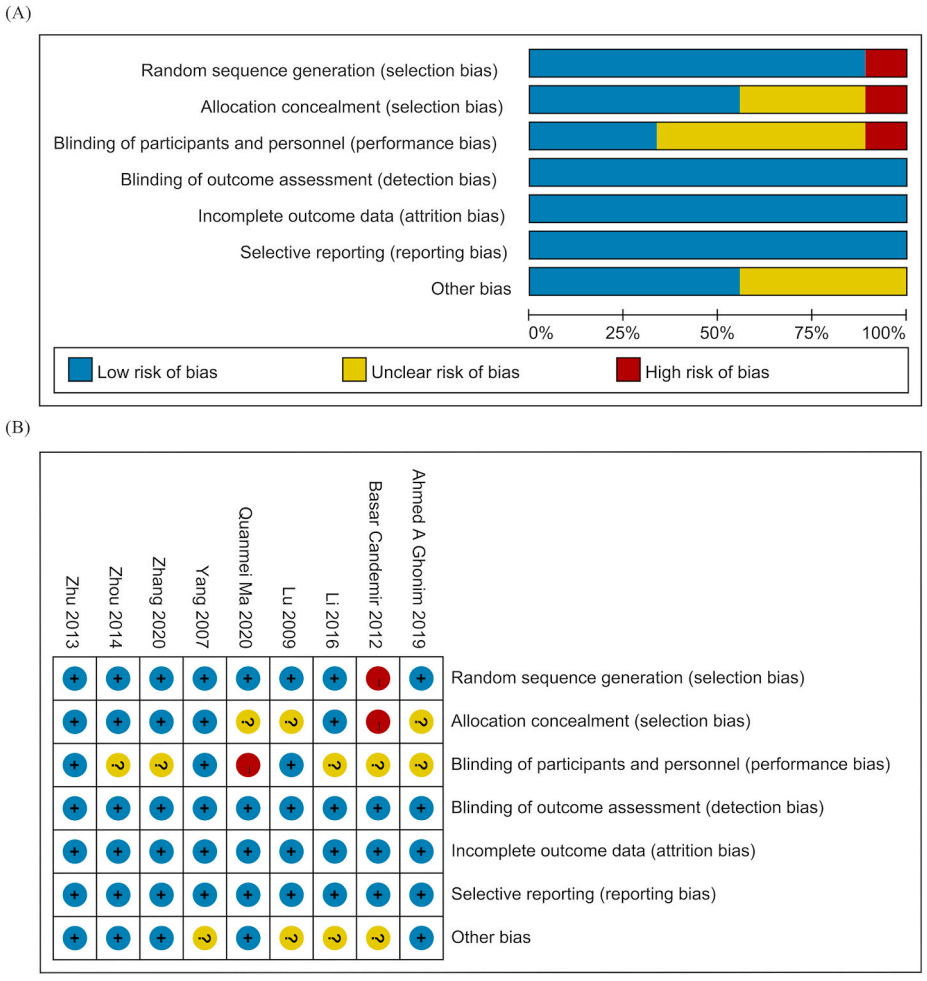

Fig. 2. Study selection diagram.

Table 1
Characteristics of the included RCTs.

No.	Study Year	Country	Study Design	Study Period	Random sequences	Blinding procedures	Primary outcome	Secondary outcome	Follow-up
1	Yang 2007	China	Single center	August to October 2006	Random number table	Single blinding	①②	③④⑤	In-hospital 30 days 3 months
2	Lu 2009	China	Single center	NA	NA	Single blinding	①②	③④⑤	In-hospital 30 days
3	Basar 2012	Turkey	Single center	NA	NA	Open-label	①	③	30 days
4	Zhu 2013	China	Multiple center	June 2006 to March 2010	Computer-generated random-allocation system	Double blinding	①②	③④⑥⑦	30 days 6 months
5	Zhou 2014	China	Single center	January 2011 to September 2012	Sealed unlabeled envelopes	NA	①②		In-hospital 30 days
6	Li 2016	China	Single center	July 2011 to September 2012	Random number table	NA	①②	③④	30 days
7	Ahmed 2019	Saudi Arabia	Single center	NA	NA	NA	①②	③④⑤⑥	In-hospital 30 days
8	Ma 2020	China	Single center	February 2016 and May 2018	NA	Open-label	②	③⑦	1 week 12 months
9	Zhang 2020	China	Single center	September 2011 to January 2017	Sealed unlabeled envelopes	NA	①	③⑤⑥	In-hospital 30 days

NA = not available, RCT = randomized controlled trial, ① = major adverse cardiovascular events, ② = bleeding events, ③ = thrombolysis in myocardial infarction grade 3 flow, ④ = thrombocytope, ⑤ = in-hospital left ventricular injection fraction, ⑥ = 30-day left ventricular injection fraction, ⑦ = 6-month left ventricular injection fraction.

vs. 73.8% (P = 0.89), 68.9% vs. 63.9% (P = 0.90), and 44.3% vs. 34.4% (P = 0.11), separately. For target vessels in IC and IV groups, the ratios of LM (left main coronary artery), LAD (left anterior descending branch), RCA (right coronary artery), and CX (circumflex artery) were 4.5% vs. 3.4% (P = 0.77), 51.5% vs. 55.2% (P = 0.27), 14.1% vs. 17.0% (P = 0.17), and 31.1% vs. 27.3% (P = 0.18), severally. Furthermore, the door-to-balloon time and number of stents were 82.9 ± 81.6 min vs. 82.8 ± 62.1 min (P = 0.08), and 1.3 ± 0.6 vs. 1.3 ± 0.5 (P = 0.83), independently. Therefore, there showed no differences in the baseline characteristics of the IC and IV administration groups.

3.3. Primary efficacy outcome

Intracoronary administration of tirofiban was significantly more effective in STEMI patients undergoing PPCI (P = 0.028), the incidence of 30-day MACE was significantly lower than that of intravenous administration, and the 30-day MACE incidence of intracoronary administration was 0.65 times that of intravenous administration (RR = 0.65, 95% CI: 0.44–0.95) (Fig. 3A). Sensitivity analysis with the 'leave-one-out approach' showed that little effect on the conclusions after removing any one of the studies (Fig. 3B). Moreover, a funnel plot was drawn to assess whether there was bias in the 8 articles involved in this study (Fig. 3C), and quantitatively detected publication bias by Egger's test (Fig. 3D), and obtained the P = 0.83 > 0.05, indicating that the funnel plot was symmetrical, and there was no publication bias in this study.

3.4. Primary safety outcome

There was no statistically significant difference (P = 0.82) in the incidence of in-hospital bleeding events between the 2 groups (RR = 0.96, 95% CI: 0.67–1.38) (Fig. 4A). Sensitivity analysis showed little effect on the conclusions after removing any one of the studies (Fig. 4B). Moreover, a funnel plot was drawn to assess whether there was bias in the 7 articles involved in this study (Fig. 4C), and quantitatively detected publication bias by Egger's test (Fig. 4D), and obtained the P = 0.65 > 0.05, indicating that the funnel plot was symmetrical, and there was no publication bias in this study.

3.5. Secondary efficacy outcome

Compared with IV, IC tirofiban had no statistically significant difference (P = 0.08) in the rate of TIMI grade 3 flow (RR = 1.13, 95% CI: 0.99–1.30). In addition, the IC tirofiban group was 2.03% higher than IV (WMD = 2.03, 95% CI: 1.03–3.02, P < 0.001) in the in-hospital LVEF and 6.01% higher in the 6-month LVEF (WMD = 6.01, 95% CI: 5.02–6.99, P < 0.001) (Funnel plots in Supplementary Figure). However, we quit carrying out the analysis of the outcome of the 30-day LVEF because of the $I^2 > 90\%$ and P < 0.001 of the Q test according to the heterogeneity test (Fig. 5A, B, C).

3.6. Secondary safety outcome

There was no statistically significant difference (P = 0.32) in the rate of thrombocytopenia between the 2 groups (RR = 0.63, 95%

Table 2
Baseline characteristics.

No.	Study Year	Patients (n)	General Data				Risk Ractors (%)			Target Vessel (%)				PCI Data (mean ± SD)	
			Age (mean ± SD)	Male (%)	Killip Class II–IV (%)	3-Vessel Disease (%)	Hypertension	Diabetes	Smoking	LM	LAD	LCX	RCA	Door-to-balloon Time	Number of Stent
1	Yang 2007	28/26	60.2 ± 13.2/ 57.2 ± 11.9	92.9/ 65.4	35.7/42.3	NA	46.4/50.0	17.9/23.1	71.4/ 50.0	14.3/ 11.5	NA	NA	NA	NA	NA
2	Lu 2009	21/22	65.0 ± 10.1/ 63.1 ± 11.4	85.7/ 86.4	28.6/27.3	NA	71.4/63.6	19.0/31.8	52.4/ 50.0	NA	NA	NA	NA	217.9 ± 164.8/ 177.9 ± 109.6	NA
3	Basar 2012	34/22	69.4 ± 8.6/ 70.9 ± 10.5	61.8/ 54.5	NA	NA	58.8/50.0	47.1/50.0	58.8/ 45.5	NA	50.0/ 54.5	32.4/ 22.7	17.6/ 22.7	NA	1.5 ± 0.8/ 1.4 ± 0.6
4	Zhu 2013	229/224	64.6 ± 11.9/ 64.7 ± 12.2	79.0/ 82.1	13.5/15.6	28.4/27.7	38.4/40.6	27.5/29.9	47.6/ 47.3	NA	52.8/ 56.7	10.5/ 12.1	32.8/ 29.0	80.7 ± 70.6/ 83.9 ± 56.6	1.2 ± 0.5/ 1.2 ± 0.4
5	Zhou 2014	84/80	60.9 ± 8.2/ 57.7 ± 6.5	77.4/ 72.5	NA	NA	76.2/71.3	21.4/18.8	NA	NA	48.8/ 47.5	14.3/ 21.3	36.9/ 31.2	NA	NA
6	Li 2016	29/29	63.8 ± 6.7/ 62.5 ± 6.0	62.1/ 58.6	NA	31.0/24.1	55.2/58.6	58.6/55.2	31.4/ 31.0	NA	51.7/ 55.1	17.2/ 17.2	31.0/ 27.5	62.6 ± 14.7/ 64.2 ± 15.1	1.5 ± 0.6/ 1.5 ± 0.6
7	Ahmed 2019	45/50	55.9 ± 11.7/ 58.6 ± 10.2	51.1/ 54.0	24.4/18.0	4.4/6.0	42.2/40.0	100.0/ 100.0	68.8/ 68.0	NA	55.6/ 60.0	11.1/ 14.0	28.8/ 20.0	44.0 ± 7.6/46.8 ± 8.9	NA
8	Ma 2020	66/66	54.0 ± 11.5/ 52.2 ± 12.9	84.8/ 81.8	9.1/7.6	NA	36.4/43.9	27.3/18.2	78.8/ 66.7	NA	NA	NA	NA	NA	NA
9	Zhang 2020	61/61	61.4 ± 9.7/ 62.8 ± 11.3	67.2/ 63.9	NA	NA	82.0/73.8	68.9/63.9	44.3/ 34.4	0.0/ 0.0	47.5/ 55.7	18.0/ 29.5	26.2/ 23.0	NA	1.2 ± 0.6/ 1.3 ± 0.6

Data are n (%), mean ± SD. NA = not available, PCI = percutaneous coronary intervention, LM = left main, LAD = left anterior descending, LCX = left circumflex artery, RCA = right coronary artery.

Table 3
Characteristics of interventions.

No.	Study Year	Preoperative Medical Therapy (%)			Intervention	
		Aspirin	Clopidogrel	Heparin	IC	IV
1	Yang 2007	100/100	100/100	100/100	intracoronary bolus of tirofiban (10 μg/kg) after the guidewire or balloon passing through the IRA and then intravenous infusion (0.15 μg/kg/min) for 36 h	intravenous bolus of tirofiban (10 μg/kg) and then intravenous infusion (0.15 g/kg/min) before PCI for 36 h
2	Lu 2009	100/100	100/100	100/100	intracoronary bolus of tirofiban (10 μg/kg) after the guidewire or balloon passing through the IRA and intravenous bolus of tirofiban (10 μg/kg) plus maintenance infusion (0.15 μg/kg/min) for 36 h	intravenous bolus of tirofiban (10 μg/kg) plus maintenance infusion (0.15 μg/kg/min) for 36 h
3	Basar 2012	100/100	100/100	100/100	intracoronary tirofiban bolus (25 μg/kg) through the guiding catheter in theIRAand then maintenance intravenous infusion of tirofiban (0.15 μg/kg/min) for 24 h	intravenous tirofiban bolus (25 μg/kg) and then maintenance intravenous infusion of tirofiban (0.15 μg/kg/min) for 24 h
4	Zhu 2013	100/100	100/100	100/100	intravenous tirofiban bolus (10 μg/kg) followed by maintenance infusion (0.15 μg/kg/min) before PCI for 24–36 h and intracoronary bolus of tirofiban (10 μg/kg) through the guide cathete proximal to the culprit lesion after restoration of antegrade blood flow with a guidewire or predilation with a small balloon	intravenous tirofiban bolus (10 μg/kg) followed by maintenance infusion (0.15 μg/kg/min) before PCI for 24–36 h and intracoronary bolus of saline (10 ml) through the guide cathete proximal to the culprit lesion after restoration of antegrade blood flow with a guidewire or predilation with a small balloon
5	Zhou 2014	100/100	100/100	NA	intracoronary bolus of tirofiban (10 μg/kg) through the guiding catheter in the IRA plus maintenance infusion (0.15 μg/kg/min) for 18–24 h	intravenous bolus of tirofiban (10 μg/kg) plus maintenance infusion (0.15 μg/kg/min) before PCI for 18–24 h
6	Li 2016	100/100	100/100	NA	intracoronary bolus of tirofiban (10 μg/kg) through the guiding catheter in the IRA plus maintenance infusion (0.15 μg/kg/min) for 36 h	intravenous bolus of tirofiban (10 μg/kg) plus maintenance infusion (0.15 μg/kg/min) before PCI for 36 h
7	Ahmed 2019	100/100	100/100	100/100	intracoronary tirofiban bolus (25 μg/kg) through the guiding catheter in theIRAand then maintenance intravenous infusion of tirofiban (0.15 μg/kg/min) for 18 h	intravenous tirofiban bolus (25 μg/kg) and then maintenance intravenous infusion of tirofiban (0.15 μg/kg/min) for 18 h
8	Ma 2020	100/100	100/100	100/100	intracoronary bolus of tirofiban (10 μg/kg) through the PCI guide catheter with subsequent intravenous infusion for 12 h (0.15 μg/kg/minute)	intravenous bolus of tirofiban (10 μg/kg) with subsequent intravenous infusion for 12 h (0.15 μg/kg/minute)
9	Zhang 2020	100/100	100/100	NA	tirofiban injection via the TA catheter to the IRA after TA plus continuous intravenous injection for 48 h	TA-only plus intravenous tirofiban injection for 48 h

NA = not available, IC = intracoronary, IV = intravenous, PCI = percutaneous coronary intervention, IRA = infarct-related artery, TA = thrombus aspiration.

CI: 0.26–1.57) (Fig. 5D). (Funnel plots in Supplementary Figure).

3.7. Sensitivity analysis

After removing any study in turn, and combining all the remaining studies to obtain the effect size (ES), except for the secondary safety outcome in-hospital LVEF, all within the 95% CI of the combined ES in the meta-analysis, indicating that individual studies had little impact on the final results, and the results of this meta-analysis were relatively stable (Supplementary Table 2) The reason may be that thrombus aspiration plus infarct-related artery (IRA) administration of tirofiban can improve myocardial perfusion and save more myocardium for better LVEF [26].

3.8. Meta-regression

Meta-regression was not assessed as there were only a small number of studies (<10).

3.9. Subgroup analysis

We divided the included studies into 10 μg/kg (low-dose group) and 25 μg/kg (high-dose group) for subgroup analysis according to the doses given intracoronary. The results of the low-dose group showed that the 30-day MACE incidence rate of IC tirofiban was lower than that of IV and there was no significant difference in the incidence (RR = 0.67, 95% CI: 0.41–1.10, P = 0.11), and the results of the high-dose group also showed that the 30-day MACE incidence rate of IC tirofiban was lower than that of IV and there was no significant difference in the incidence (RR = 0.61, 95% CI: 0.32–1.14, P = 0.12), but the overall results showed that the 30-day MACE event rate in

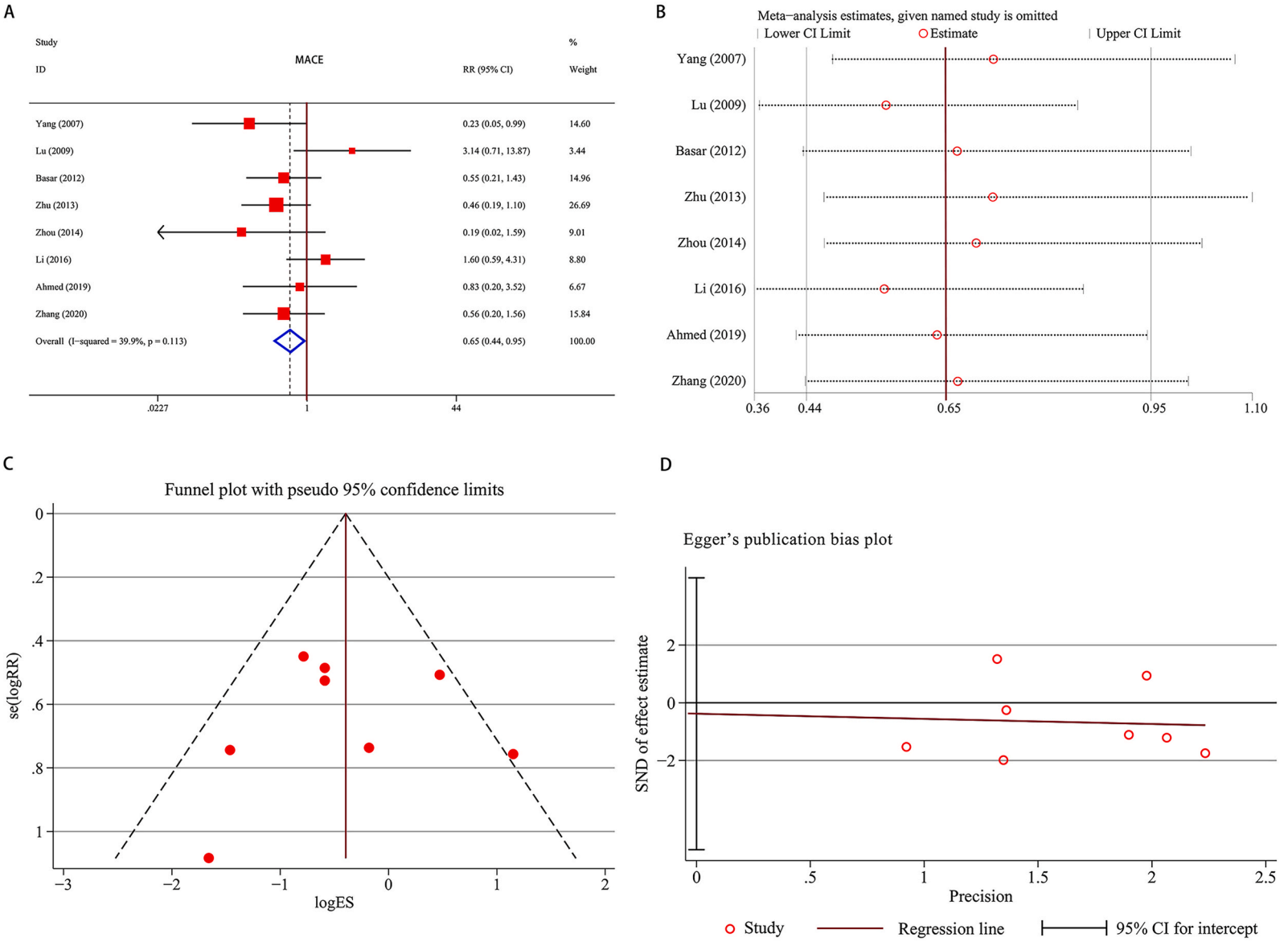

Fig. 3. Analysis results of intracoronary versus intravenous tirofiban in STEMI patients undergoing PPCI in 30-day MACE. (A). Forest plot of 30-day MACE based on the Mantel-Haenszel fixed effects model. (B). Sensitivity analysis of 30-day MACE. (C). Funnel plot of 30-day MACE. (D). Egger's publication bias plot of 30-day MACE.

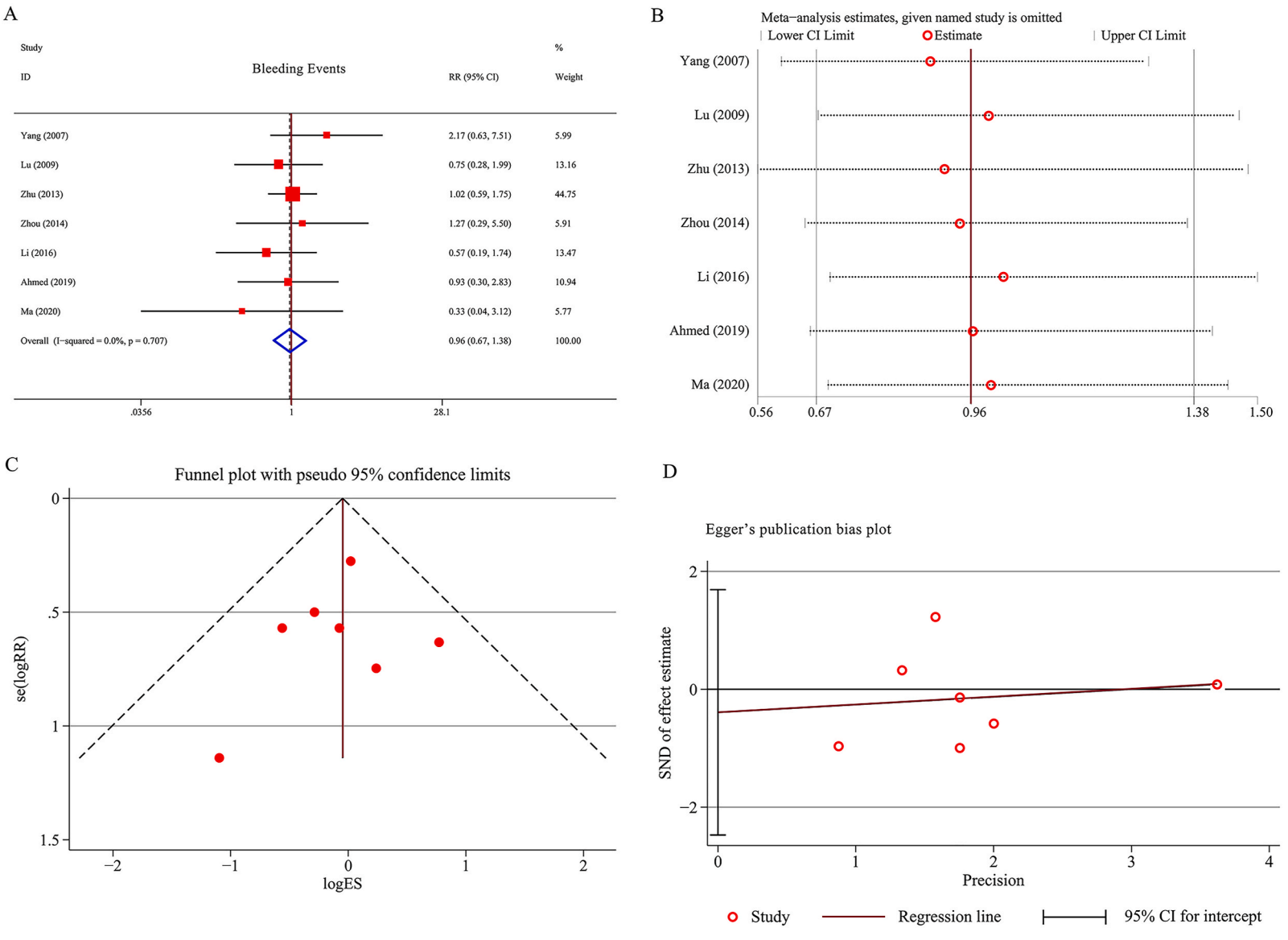

Fig. 4. Analysis results of intracoronary versus intravenous tirofiban in STEMI patients undergoing PPCI in bleeding events. (A). Forest plot of bleeding events based on the Mantel-Haenszel fixed effects model. (B). Sensitivity analysis of bleeding events. (C). Funnel plot of bleeding events. (D). Egger's publication bias plot of bleeding events.

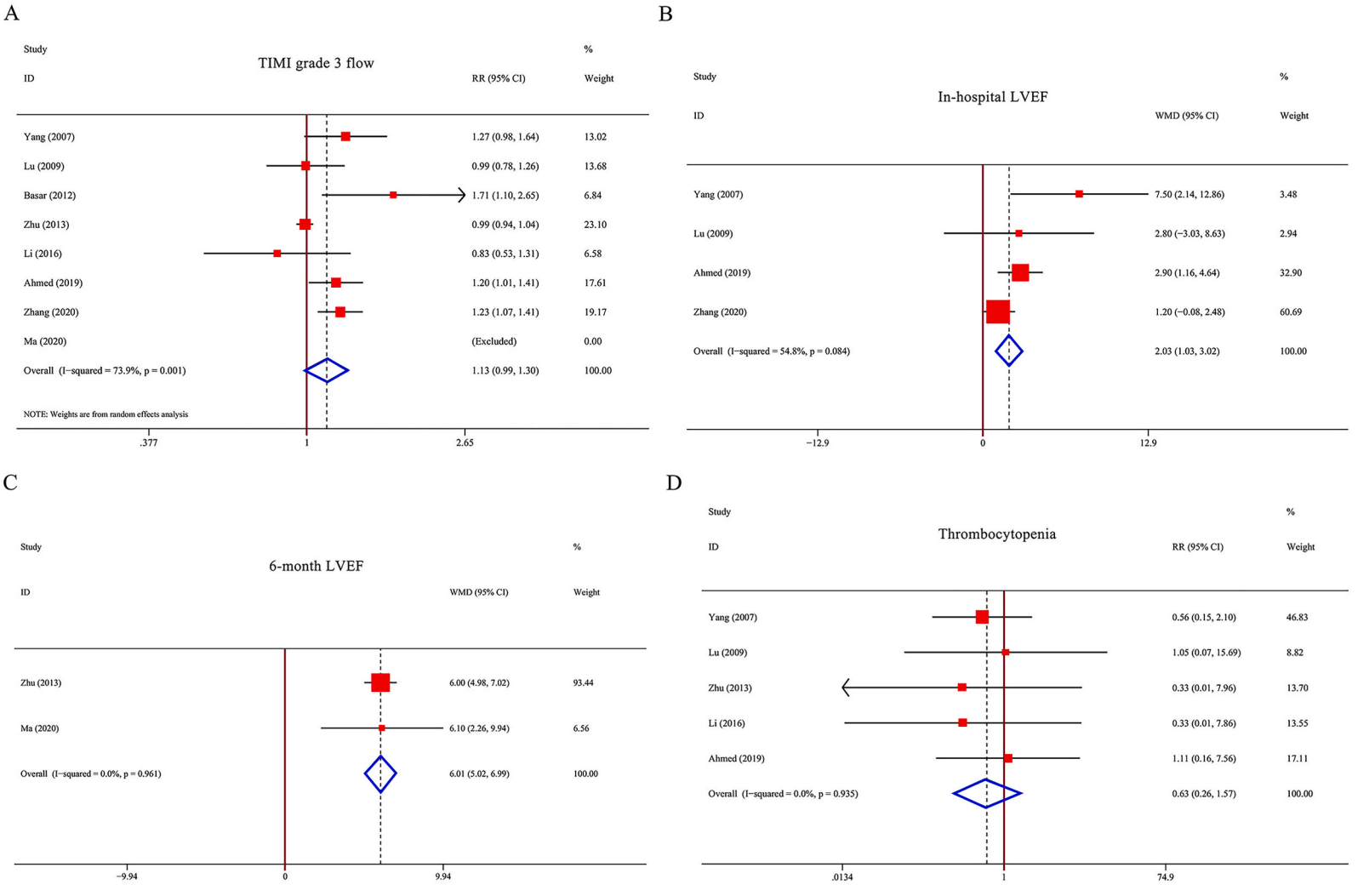

Fig. 5. Forest plot of secondary outcomes in STEMI patients treated with intracoronary versus intravenous tirofiban. (A). Forest plot of TIMI grade 3 flow based on the DerSimonian-Laird random effects model. (B). Forest plot of in-hospital LVEF based on the DerSimonian-Laird random effects model. (C). Forest plot of 6-month LVEF based on the Mantel-Haenszel fixed effects model. (D). Forest plot of thrombocytopenia based on the Mantel-Haenszel fixed effects model.

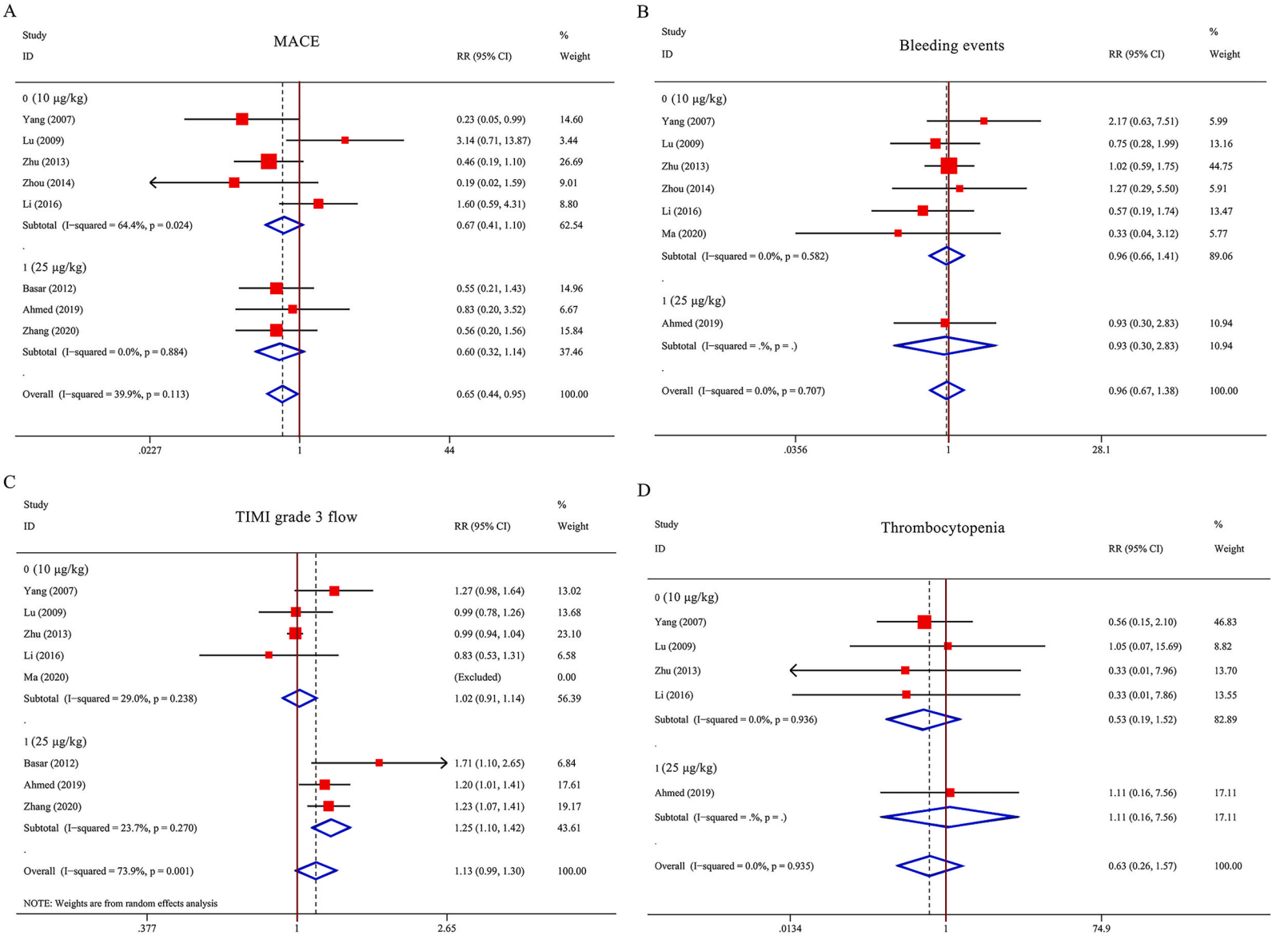

Fig. 6. Subgroup analysis of different intracoronary doses of tirofiban in several outcomes. (A). 30-day MACE, (B). Bleeding events, (C). TIMI grade 3 flow, and (D). Thrombocytopenia.

the IC group was significantly lower than that in the IV group and was statistically significant (RR = 0.65, 95% CI: 0.44–0.95, P = 0.028). This suggests that with increasing sample size, IC tirofiban significantly reduces the incidence of postoperative 30-day MACE in STEMI patients, independent of the doses of IC tirofiban (Fig. 6A). However, for the incidence rate of bleeding events and thrombocytopenia, there was no significant difference between IC and IV (Fig. 6B, D). In addition, for TIMI grade 3 flow, subgroup analysis showed no difference between low-dose groups (RR = 1.02, 95% CI: 0.91–1.14, P = 0.77), but it is worth noting that the significant reduction in heterogeneity between the two groups (RR = 1.13, 95% CI: 0.99–1.30, P = 0.001) suggests that the different intracoronary doses may be the source of high heterogeneity and that TIMI grade 3 flow in the high-dose group IC group is better than that in the IV group (Fig. 6C). Due to the insufficient included studies, we did not perform a subgroup analysis of LVEF.

4. Discussion

In this meta-analysis, a total of 1177 STEMI patients undergoing PPCI and receiving tirofiban concurrently in 9 RCTs, were randomized into the IC tirofiban group and IV tirofiban group. The IC strategy was associated with a 35% reduction in the incidence of 30-day MACEs, and improved in-hospital and 6-month LVEFs. There were no significant differences in bleeding events, TIMI grade 3 flow after PPCI and thrombocytopenia between the two groups. Our study suggests that IC tirofiban may be a more effective and safe option for STEMI patients undergoing PPCI.

Treatment options for STEMI are still evolving rapidly and include PPCI with drug-eluting stent implantation, thrombosis aspiration (TA), coronary rotational atherectomy (CRA), etc. Rapid reperfusion with PPCI within 120 min can reduce cardiac mortality rates compared to conventional thrombolysis therapy [27]. GPIs are currently regarded as the effective platelet aggregation inhibitors. Because of the shortened time from symptom onset to coronary angiography has been rapidly shortened and the wide application of dual antiplatelet therapy (DAPT), the benefits of administration of GPIs has been weakened than before [28]. The 2017 European Society of Cardiology (ESC) guideline for the management of acute myocardial infarction (AMI) patients shows that IV GPIs are no longer recommended in standard treatment strategies of STEMI patients undergoing PPCI, because the IV administration of GPIs cannot provide benefit but increases the risk of bleeding events [29]. However, the 2021 ACC/AHA guideline for coronary artery revascularization remommends IV GPIs in ACS patients undergoing PCI with large thrombus burden, slow flow, or no-reflow [30]. Furthermore, the related meta-analyses suggest that routine administration of GPIs in STEMI patients reduces mortality due to a reduction in recurrent ischaemic events, and IC tirofiban improves short-term outcomes in ACS patients treated with PCI without increasing bleeding rate, which is consistent with our conclusions [31,32]. For these STEMI patients undergoing PPCI, the routine use of GPIs as adjuvant therapy can significantly reduce the incidence of recurrent ischemic events including recurrent MI, repeat revascularization, and no-reflow phenomenon, thereby reducing the risk of death [33]. However, GPIs often lead to adverse reactions such as bleeding and thrombocytopenia at the same time.

Compared with other GPIs, tirofiban has the following advantages. Tirofiban was non-inferior to abciximab in ST-segment elevation recovery after coronary intervention [34], and there was no significant difference in the rate of all-cause mortality, MACE, and bleeding events between tirofiban and abciximab groups, while the tirofiban group had a lower incidence of moderate or severe thrombocytopenia [10,35,36]. In addition, FABOLUS FASTER Trial showed that tirofiban provided stronger inhibition of platelet aggregation (IPA) than cangrelor in STEMI patients undergoing PPCI [37]. Furthermore, compared with eptifibatide, tirofiban can enable ACS patients with PCI to achieve better coronary filling without any difference in improving myocardial microcirculation perfusion, inhibiting platelet aggregation rate, reducing platelet-monocyte interaction and safety [38]. Tirofiban is also more widely used in clinical practice by virtue of its own economic advantages.

A meta-analysis of randomized trials concluded that early routine use of tirofiban in combination with dual antiplatelet therapy (DAPT) can reduce the incidence of MACE events without increasing the rate of major bleeding in STEMI patients with PPCI [39], the On-TIME 2 study showed that upstream high-dose tirofiban can provide higher initial patency and ST-segment resolution (STR) [40], and the FINESSE study showed lower rates of bleeding in STEMI patients treated with GPI in the catheterization laboratory [41]. In clinical practice, interventional cardiologists prefer to prolong the maintenance time of GPIs, so as to continue to fully inhibit thrombosis and improve microvascular perfusion [33]. Given the lack of sufficient and reliable clinical data to validate standard treatment for GPIs, the 2021 ACC guidelines merely recommend intravenous administration of GPIs for at least 18 h in high-risk or thrombus-burdened situations (class IIa) [29,30]. In terms of maintenance time, the latest research showed that the maintenance time of tirofiban for $<$24 h and $\geq$24 h had similar clinical effects, there was no significant difference in the incidence of MACE, cardiac function, and in-hospital bleeding events between the two groups of patients, indicating that the maintenance time of tirofiban can be appropriately shortened [42]. Nevertheless, there is no recommendation for a specific route of administration and further exploration of specific methods of use is needed to maximize clinical benefits, therefore, we conducted this meta-analysis to find the more efficient and safer administration of tirofiban.

IC and IV are two different methods used for the administration of tirofiban. Intracoronary administration is commonly used for interventional cardiac procedures and refers to intracoronary bolus of tirofiban after the guidewire or balloon passing through the infarct-related artery, followed by intravenous maintenance infusion. In contrast, intravenous administration refers to the administration of tirofiban into a vein, including intravenous bolus of tirofiban followed by intravenous maintenance infusion, and intravenous maintenance infusion of tirofiban only. The results of this meta-analysis showed that IC tirofiban compared with IV significantly reduces the incidence of 30-day MACE in STEMI patients undergoing PPCI without increasing bleeding risk. This is consistent with the results of a previous meta-analysis evaluating the clinical benefit of IC tirofiban compared to IV in ACS patients undergoing PPCI [43], indicating that administration by the intracoronary route is safe and effective in providing favorable clinical outcomes [44]. IC tirofiban can significantly increase local platelet GP IIb/IIIa receptor occupancy (RO) [45]. Moreover, although tirofiban can reach the

effective blood drug concentration within 5 min through the peripheral intravenous route, the effective blood drug concentration will be greatly reduced in the coronary artery due to the "first pass elimination" effect of the liver [46]. IC can substantially increase the concentration of tirofiban at the IRA compared to IV administration, this is well explained the result of subgroup analysis that TIMI grade 3 flow in the high-dose group IC group is better than that in the IV group. Since tirofiban and eptifibatide have similar mechanisms of action, both are inhibitors of competitive fibrinogen binding to platelet GP IIb/IIIa receptors, so local high concentrations of the drug may lead to thrombus disintegration in the microcirculation and dissociate bound fibrinogen, leading to ruptured plaque and thrombus disintegration in the microcirculation [45]. In addition, in the culprit atherothrombotic lesions, intracoronary injection of tirofiban can effectively alleviate microvascular occlusion through endothelial protection, and at the same time, the significant reduction of P-selectin, vWF, CD40 ligand (CD40L), and serum amyloid A (SAA) levels in coronary sinus also indicated that local platelet aggregation and inflammatory process were significantly reduced, thus achieving the purpose of rapidly inhibiting activated platelets and ultimately reduce the incidence of MACE events [47,48].

Tirofiban-induced thrombocytopenia (TIT) is a type of drug-induced immune thrombocytopenia (DITP), the pathogenesis may be that after tirofiban binds to glycoprotein IIb/IIIa, its conformation changes and then a new antigenic determinant which binds to antiplatelet antibodies in the blood is formed so that platelets are recognized and cleared by the reticuloendothelial cell system or liver [49]. It can be seen that the mechanism of TIT is an autoimmune reaction, which has little to do with the route of administration, therefore, it is logical that there was no statistical difference in the incidence of TIT between the IC and IV groups. In terms of LVEF, we found that intracoronary tirofiban ameliorated the in-hospital and 6-month LVEF in these STEMI patients after PPCI, suggesting that intracoronary administration of tirofiban may reduce the incidence of MVO compared with the intravenous group to improve LV remodeling [50].

5. Limitations

There are some limitations in this meta-analysis. First, a multicenter study based on an Asian population showed that the frequency of using GPIs in ACS patients undergoing PPCI was higher in STEMI patients than in NSTEMI (non-ST-segment elevation myocardial infarction) and UA (unstable angina) patients [51], but the comparison of the efficacy of tirofiban in STEMI patients of different races remained to be verified. Second, the number of RCTs included in this study was limited, and the high-quality literature included was limited as well, these factors may potentially affect the final results. Third, the dosage and maintenance time of drug administration and whether heparin was used would have a certain influence on the outcome indicators, but there were many interference factors, which were not within the scope of this study. Fourth, regarding the outcomes of TIMI and all LVEFs, there was some statistical and baseline heterogeneity between studies, and to overcome these limitations as much as possible, we used the random-effects model for these outcomes. Fifth, there were slight differences in follow-up time, and the included trials were conducted at different time periods.

6. Conclusion

In STEMI patients undergoing PPCI, the IC tirofiban regimen compared with IV significantly reduced the 30-day MACE incidence and improved the in-hospital and 6-month LVEF without increasing the risk of bleeding or thrombocytopenia.

Author contribution statement

Rui Tian and Rugang Liu: Performed the study and wrote the paper. Xiaoxing Li: Analyzed and interpreted the data. Jiajun Zhang and Yong Li: Performed the study. Feng Xu: Contributed analysis tools and data. Shujian Wei: Analyzed and interpreted the data and wrote the paper. Chuanbao Li: Conceived and designed the study.

Funding statement

Supported by the National Natural Science Foundation of China (82070388, 82170442), National Natural Science Foundation of Shandong Province (ZR2020MH035), and Taishan Qingnian Scholar Program of Shandong Province (tsqn202211310).

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgements

Thank all the team members for their help and discussion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15842.

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