

Original Article

Efficacy and safety of tirofiban in patients with non-ST segment elevation acute coronary syndromes: a systemic review and meta-analysis

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Received March 18, 2016; Accepted June 12, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Objective: This study aims to systemically evaluate the efficacy and safety of tirofiban in patients with non-ST segment elevation acute coronary syndromes (NSTEMI/ACS). Methods: The randomized controlled trials (RCTs) and cohort studies were searched from PubMed and Ovid until Mar. 2016, chosen and extracted by 2 reviewers independently, and cross-checked and assessed in the quality and methodology. All data were given meta-analysis by using stata software 11.0. Results: A total of 19 documents with 8582 patients were finally enrolled. The primary endpoint showed that, there was no difference in all-cause mortality between NSTEMI/ACS patients treated with tirofiban compared with those treated with placebo or others (RR=0.80, 95% CI: 0.64 to 1.01, P=0.066, P for heterogeneity =0.85, I²=0%). The second endpoint showed that tirofiban reduced the occurrence of the composite of major adverse cardiovascular events (MACE) both in-hospital follow-up (RR=0.76, 95% CI: 0.61 to 0.96, P=0.018, P for heterogeneity =0.069, I²=40.8%), 30-day follow-up (RR=0.71, 95% CI: 0.59 to 0.85, P=0.000, P for heterogeneity =0.006, I²=58.2%) and ≥ 3-month follow-up (RR=0.65, 95% CI: 0.48 to 0.86, P=0.003, P for heterogeneity =0.007, I²=75.2%), as compared with control group, and the differences were statistically significant. The safety endpoint showed tirofiban was associated with higher bleeding risk (RR=1.31, 95% CI: 0.13 to 1.51, P=0.000, P for heterogeneity =0.997, I²=0%) in NSTEMI/ACS patients compared with the control group. Conclusion: Tirofiban has a definite role in improving the outcomes of patients with non-ST segment elevation acute coronary syndromes. However, treatment with tirofiban provided no significant benefit on all-cause mortality in NSTEMI/ACS patients. Furthermore, tirofiban was associated with higher bleeding risk in NSTEMI/ACS patients. However, no fatal bleeding was observed in included studies. This study demonstrated that as a new generation of antiplatelet drugs, the early application of tirofiban can effectively and safely improve outcomes in NSTEMI/ACS patients.

Keywords: Tirofiban, NSTEMI/ACS, meta-analysis

Introduction

Non-ST segment elevation acute coronary syndromes (NSTEMI/ACS) clinically includes unstable angina and non-ST segment elevation myocardial infarction (NSTEMI). The early and strong inhibition of activated platelet plays a vital role in preventing serious thromboembolic complication for these patients. At present, the drug commonly used to prevent thrombosis is combined use of both aspirin and clopidogrel. However, these drugs are partially effective. Recently, antagonists to platelet glycoprotein IIb/IIIa (GPIIb/IIIa) have been found to be useful in the treatment of patients with NSTEMI/ACS. In the

last years, large interest has been focused on the adjunctive administration of tirofiban, a specific non-peptide antagonist of the platelet GPIIb/IIIa receptor. The administration of tirofiban has been incorporated in clinical practice for the treatment of patients with non-ST segment elevation acute coronary syndromes. Lately, several studies [1-3] showed that GPIIb/IIIa inhibitors improves outcome and decreased the need for revascularization in NSTEMI/ACS patients with or without any coronary intervention. However, various studies [4-7] showed that the adjunctive treatment with tirofiban does not confer any clinical benefit, as compared with placebo or other antiplatelet drugs,

such as abciximab, ticagrelor. Thus, controversy still existed in the clinical efficacy of tirofiban on non-ST segment elevation acute coronary syndromes. The aim of this study was to systematically evaluate the efficacy and safety of tirofiban in patients with non-ST segment elevation acute coronary syndromes.

Materials and methods

Search strategy

The RCTs and cohort studies were searched from PubMed and Ovid until Mar. 2016. The language of publication was restricted to English. The subject terms used for this study were: Acute coronary artery syndrome (ACS), Non-ST-segment Elevation Myocardial Infarction (NSTEMI), Unstable Angina Pectoris (UAP), Percutaneous Coronary Intervention (PCI), Coronary Revascularization, Coronary Angiography (CAG), Coronary Artery Bypass Grafting (CABG) and tirofiban. We also carefully scanned the references of relevant publications to identify further publications. Two reviewers independently screened the titles and abstracts to assess their eligibility. Full texts of potentially eligible citations were retrieved for detailed examination.

Criteria for considering studies

The inclusion criteria were: 1) RCTs or cohort studies; 2) the study sample was restricted to tirofiban-treated patients with non-ST segment elevation acute coronary syndromes; 3) at least one of groups treated with placebo or others was mentioned to be as the control group; 4) complete end point data available; and 5) the study included an available clinical database. The exclusion criteria included: 1) patients were diagnosed with other type of ACS such as ST-elevation myocardial infarction (STEMI); 2) a lack of follow-up outcome data; 3) duplicate reporting came from a same trail.

Outcome measures

The primary endpoint was all-cause death. The secondary endpoint was the composite of major adverse cardiovascular events (MACE) (death, myocardial infarction, refractory ischemia, stroke and other phenomena). The safety endpoint was bleeding risk including major bleeding events, minor bleeding events and thrombocytopenia.

Data extraction

The RCTs and cohort studies were chosen and extracted by 2 reviewers independently according to inclusion and exclusion criteria, and then cross-checked. Disagreements regarding extracted data were resolved by discussion among the authors. If necessary, a third author was required to assess the remaining disagreements. Data extracted included information about: 1) baseline of the included studies (author, year, country, age, gender, comparison); 2) trial design, sample size, blinding, usage of tirofiban, follow-up, all-cause death, MACE and bleeding risk of the included studies. We contacted corresponding authors via e-mail to request further information when necessary.

Quality assessment

We evaluated the quality of RCTs by using the modified Jadad score including random sequence production (2 points), allocation concealment (2 points), blind method (2 points) and withdrawal (1 point). The total score is 7 points, and the low-quality studies are 1-3 points, the high-quality studies are 4-7 points. We evaluated the quality of cohort studies by the Newcastle-Ottawa Scale (NOS) [8-10], which is applied to assess the quality of cohort studies in meta-analysis, including selection, comparability, exposure and outcome. The total score is nine points. The quality of each included trial was assessed individually by two investigators, and discrepancies were resolved through discussion.

Statistical analysis

All data were given meta-analysis by using stata software 11.0. Tests for heterogeneity were performed with chi-squared tests. The degree of heterogeneity across the results of different studies was quantitatively assessed by the I^2 statistic, with $I^2 < 30\%$ indicating low heterogeneity, $I^2=30-50\%$ indicating moderate heterogeneity, and $I^2 > 50\%$ indicating substantial heterogeneity [11]. We performed fixed effect model for no conspicuous heterogeneity, while performed random effect model for substantial heterogeneity. In case of heterogeneity, we attempted to identify and explain it by using subgroup analysis. The results were summarized in the form of relative risk (RR) and 95%

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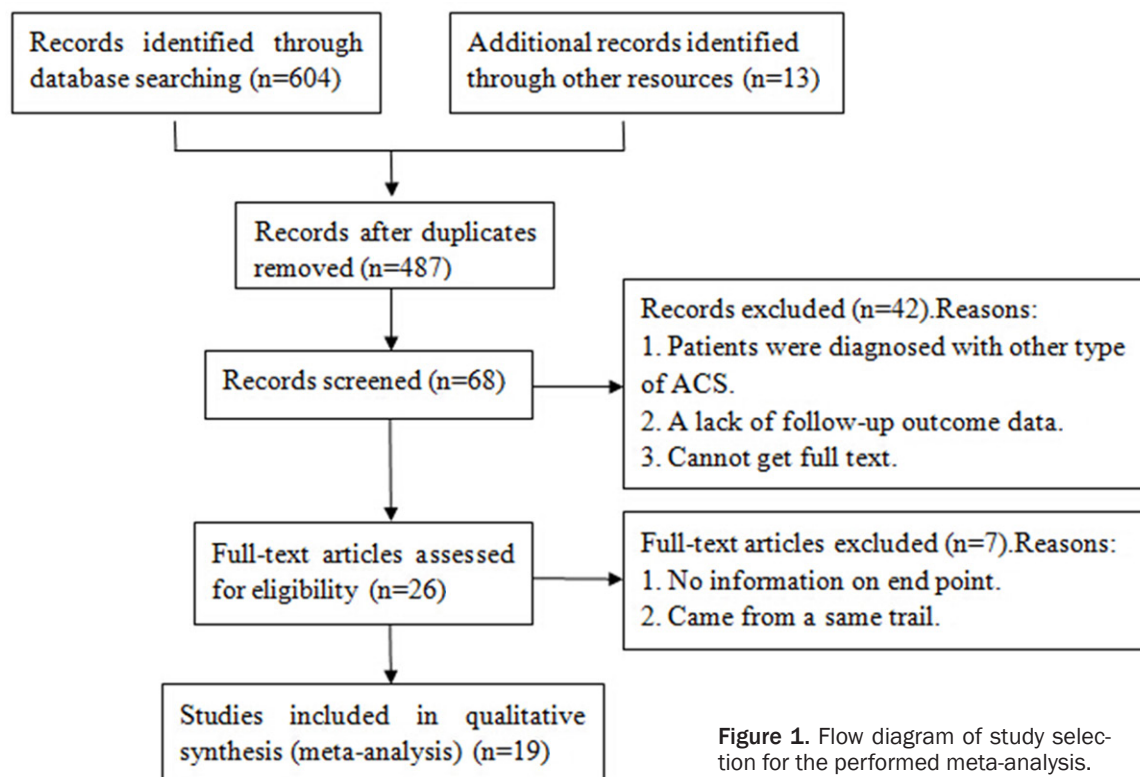


Figure 1. Flow diagram of study selection for the performed meta-analysis.

confidence interval (CI). *P* values were considered statistically significant for $P < 0.05$. Funnel plots, begg's test and egger's test were performed for assessing publication bias. Sensitivity analysis was also performed in the form of diagram.

Results

Literature search and study selection

An initial search of relevant articles yielded 617 potential literature citations. After reading the titles, abstracts and full texts, a total of 19 trails were finally included. Flow diagram of study selection for the performed meta-analysis was shown in **Figure 1**.

Overall study characteristics

Baseline and outcome message of the included studies were shown in **Tables 1** and **2**, respectively. A total of 8582 patients were included, of whom 4118 (48%) were in the tirofiban group, and 4464 (52%) were in the control group. Sixteen [12-18, 20, 21, 23, 24, 26-30] of included studies were RCTs, while two [19, 25] were retrospective cohort studies,

and just one study [22] was prospective cohort. The 19 studies came from Korea [12, 24], China [13, 17, 20], France [14], Indian [15], Italy [16, 18, 21, 22], USA [19], Netherlands [23, 27], Spain [25], Turkey [26, 28], Canada [29] and New Zealand [30], respectively. The median follow-up for the 8582 patients examined in this analysis ranged from in-hospital to 4.1 years.

Tirofiban treatment and control characteristics

Patients in control group were treated with placebo, ticagrelor, clopidogrel or eptifibatide, while treated with tirofiban in tirofiban group. The dose of tirofiban varied between low (0.4 $\mu\text{g}/\text{kg}/\text{min}$ tirofiban with intravenous injection for 30 min, followed by 0.1 $\mu\text{g}/\text{kg}/\text{min}$ for 24 to 72 h), intermediate (bolus of 10 $\mu\text{g}/\text{kg}$ tirofiban with intravenous injection for 3 min, followed by 0.1-0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 24 h) and high (bolus of 25 $\mu\text{g}/\text{kg}$ administered over 3 min followed by an infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 14 to 24 h). Low-dose tirofiban was used in thirteen studies [12, 14, 15, 18, 20, 21, 24-30], while intermediate-dose was used in three studies [13, 17, 23], and high-dose was used in three studies [16, 19, 22].

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Table 1. Baseline of the included studies

	Author, year	Design	Country	Comparison	Usage of tirofiban	Age, y	Female-no
1	Kim JS, 2015	RCT	Korea	Tirofiban/ticagrelor	0.4 µg/kg/min tirofiban with intravenous injection for 30 min, followed by 0.1 µg/kg/min for more than 24 h	62.0±10.6/59.7±11.0	13/12
2	Liu N, 2015	RCT	China	Tirofiban/placebo	10 µg/kg tirofiban with intravenous injection for 3 min, followed by 0.1 µg/kg/min for 24 h	57.8±5.1/57.3±4.8	15/14
3	Reuter PG, 2015	RCT	France	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by 0.1 µg/kg/min until PCI	63.9/66.5	25/23
4	Bhattacharya R, 2010	RCT	Indian	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by 0.1 µg/kg/min for 48 h i.v.	62.6±8.3/62.7±8.0	62/76
5	Valgimigli M, 2009	RCT	Italy	Tirofiban/placebo	a bolus of 25 µg/kg/3 min, followed by an infusion of 0.15 µg/kg/min for 14-24 h	68.6/69.2	34/36
6	Yan Z, 2009	RCT	China	Tirofiban/placebo	10 µg/kg over 3 minutes, followed by continuous infusion at a rate of 0.15 µg/kg/min for 24 h	62.8±7.6/64.1±5.4	30/36
7	Solinas E, 2009	RCT	Italy	Tirofiban/clopidogrel	0.4 µg/kg/min over 30 min plus 0.15 µg/kg/min over 24 h	66.1±10.1/64.3±10.3	6/6
8	Marmur JD, 2008	RC	USA	Tirofiban/eptifibatide	25 µg/kg tirofiban bolus-only	62.2±10.2/61.9±11	135/294
9	Song Y, 2007	RCT	China	Tirofiban/placebo	0.4 µg/kg/min of tirofiban for 30 min, followed by 0.1 µg/kg/min for 2-5 d	/	/
10	Leoncini M, 2005	RCT	Italy	Tirofiban/placebo	0.4 µg/kg/min in 30 min, followed by infusion of 0.1 µg/kg/min	65±11/67±11	29/29
11	Danzi GB, 2006	PC	Italy	Tirofiban/abciximab	25 µg/kg bolus followed by an 18-h infusion of 0.15 µg/kg/min	66±10/65±10	49/44
12	Rasoul S, 2006	RCT	Netherlands	Tirofiban/placebo	10 µg/kg bolus, 0.15 mg/kg/min maintenance	62±11/65±10	49/46
13	Kim JH, 2005	RCT	Korea	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by infusion of 0.1 µg/kg/min	59/62.8	27/29
14	Corominas N, 2004	RC	Spain	Tirofiban/eptifibatide	0.4 µg/kg/min for 30 min, followed by infusion of 0.1 µg/kg/min	66±2	19
15	Bayturan O, 2004	RCT	Turkey	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by infusion of 0.1 µg/kg/min for 72 h	59.77±11.6/59.11±6.3	10/6
16	van 't Hof AW, 2003	RCT	Netherlands	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by infusion of 0.1 µg/kg/min for 24 h	65±11/63±11	35/30
17	Okmen E, 2003	RCT	Turkey	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by infusion of 0.1 µg/kg/min for 48 h	57±12/55±14	8/13
18	Théroux, 1998	RCT	Canada	Tirofiban/placebo	0.4 µg/kg/min for 30 min, followed by infusion of 0.1-0.15 µg/kg/min	6312/6312	255/255
19	White HD, 1998	RCT	New Zealand	Tirofiban/heparin	0.6 µg/kg/min for 30 min, followed by infusion of 0.15 µg/kg/min for 47.5 h	62.511.2/62.411.1	528/504

RCT, randomized controlled trial; RC, retrospective cohort; PC, prospective cohort.

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Table 2. Outcome message of the included studies

	Author, year	No.	Follow-up	30-day death-No	MACE-No.	bleeding risk -No.	PCI	Quality
1	Kim JS, 2015	48/47	In-hospital	0/0	0/0	2/0	Yes	5
2	Liu N, 2015	45/45	In-hospital	/	3/21	7/10	No	3
3	Reuter PG, 2015	83/86	4.1 y	13/14	30 d: 2/21	2/1	Yes	6
4	Bhattacharya R, 2010	136/165	3 m	4/5	30 d: 47/94; 3 m: 77/138	32/28	No	7
5	Valgimigli M, 2009	132/131	30 d	0/1	27/46	3/2	Yes	7
6	Yan Z, 2009	120/120	6 m	1/3	30 d: 4/13; 6 m: 10/29	5/4	Yes	7
7	Solinas E, 2009	20/20	In-hospital	/	16/15	/	Yes	5
8	Marmur JD, 2008	292/584	In-hospital	0/0	10/22	9/12	Yes	9
9	Song Y, 2007	101/99	30 d	1/3	In-hospital: 6/13; 30 d: 14/29	13/7	No	5
10	Leoncini M, 2005	150/150	30 d	2/3	In-hospital: 12/11; 30 d: 14/15	3/2	Yes	7
11	Danzi GB, 2006	140/162	30 d	0/0	In-hospital: 4/6; 30 d: 9/14	5/4	Yes	9
12	Rasoul S, 2006	162/166	30 d	1/1	74/92	20/16	Yes	7
13	Kim JH, 2005	80/80	6 m	1/1	In-hospital: 1/3; 30 d: 2/5; 6 m: 8/19	8/5	Yes	5
14	Corominas N, 2004	37/19	In-hospital	/	17/8	4/1	Yes	9
15	Bayturan O, 2004	31/26	In-hospital	0/2	1/2	/	No	3
16	Van't Hof AW, 2003	111/109	30 d	5/3	11/10	15/9	Yes	5
17	Okmen E, 2003	41/42	In-hospital	0/0	24/32	3/3	Yes	3
18	Thérroux, 1998	773/797	6 m	53/56	In-hospital: 44/62; 30 d: 143/178; 6 m: 214/256	97/77	Yes	7
19	White HD, 1998	1616/1616	30 d	37/58	In-hospital: 61/90; 30 d: 257/276	137/111	Yes	7

MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

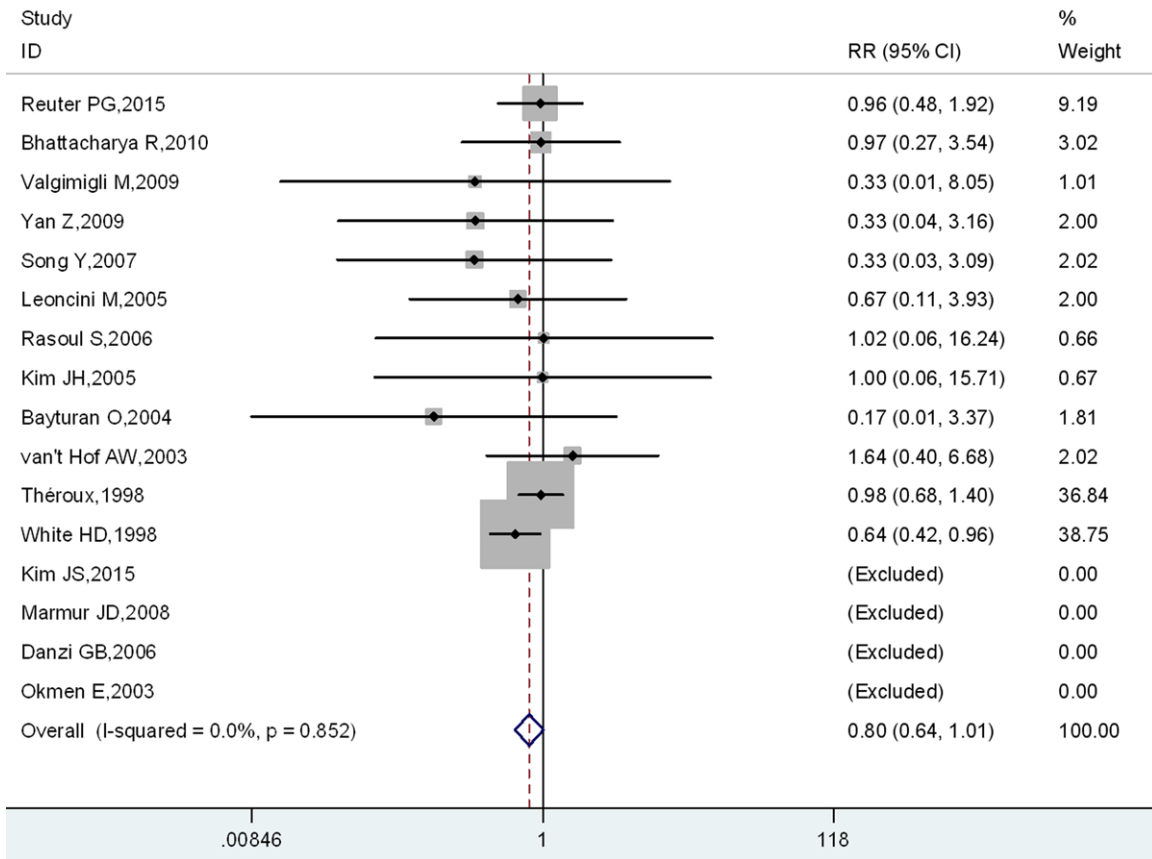


Figure 2. Forest plot of mortality of tirofiban in NSTEMI ACS patients.

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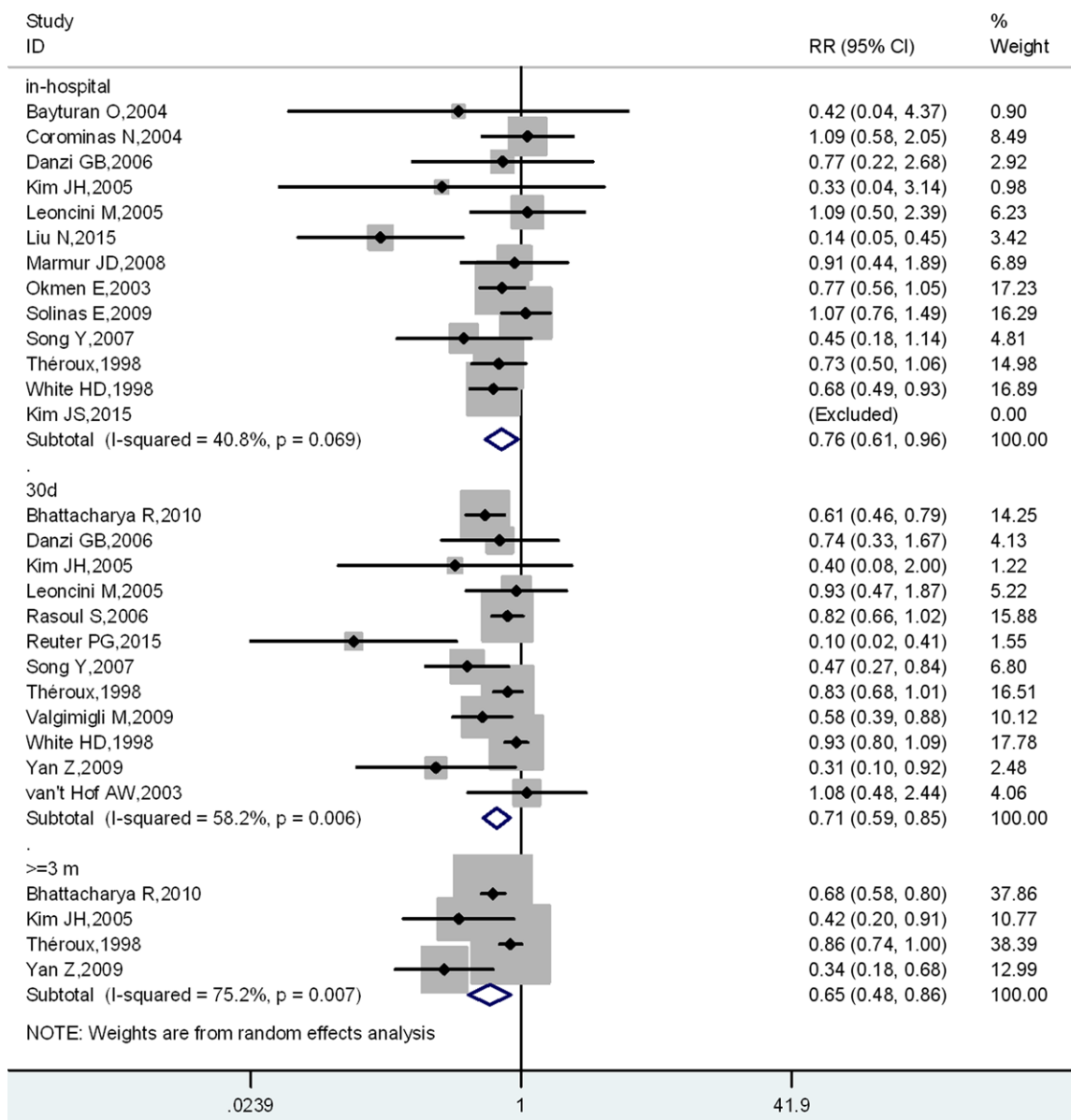


Figure 3. Forest plot of efficacy of tirofiban in NSTEMI ACS patients.

Methodological quality

Thirteen RCTs were classified as high-quality, of which seven [15-17, 21, 23, 29, 30] had a Jadad score of 7, one [14] had a Jadad score of 6 and five [12, 18, 20, 24, 27] had a Jadad score of 5. Three [13, 26, 28] studies received a Jadad score of 3, classified as low-quality. The whole three cohort studies [19, 22, 25] got nine scores by the Newcastle-Ottawa Scale (NOS).

Mortality

Data on all-cause death were available in 16 studies including 8396 patients. There was no difference in all-cause mortality between NSTEMI ACS patients treated with tirofiban compared with those treated with placebo or others (RR=0.80, 95% CI: 0.64 to 1.01, P=0.066, P for heterogeneity =0.85, I²=0%) (Figure 2). Obviously, there was no formal signal of heterogeneity across included studies.

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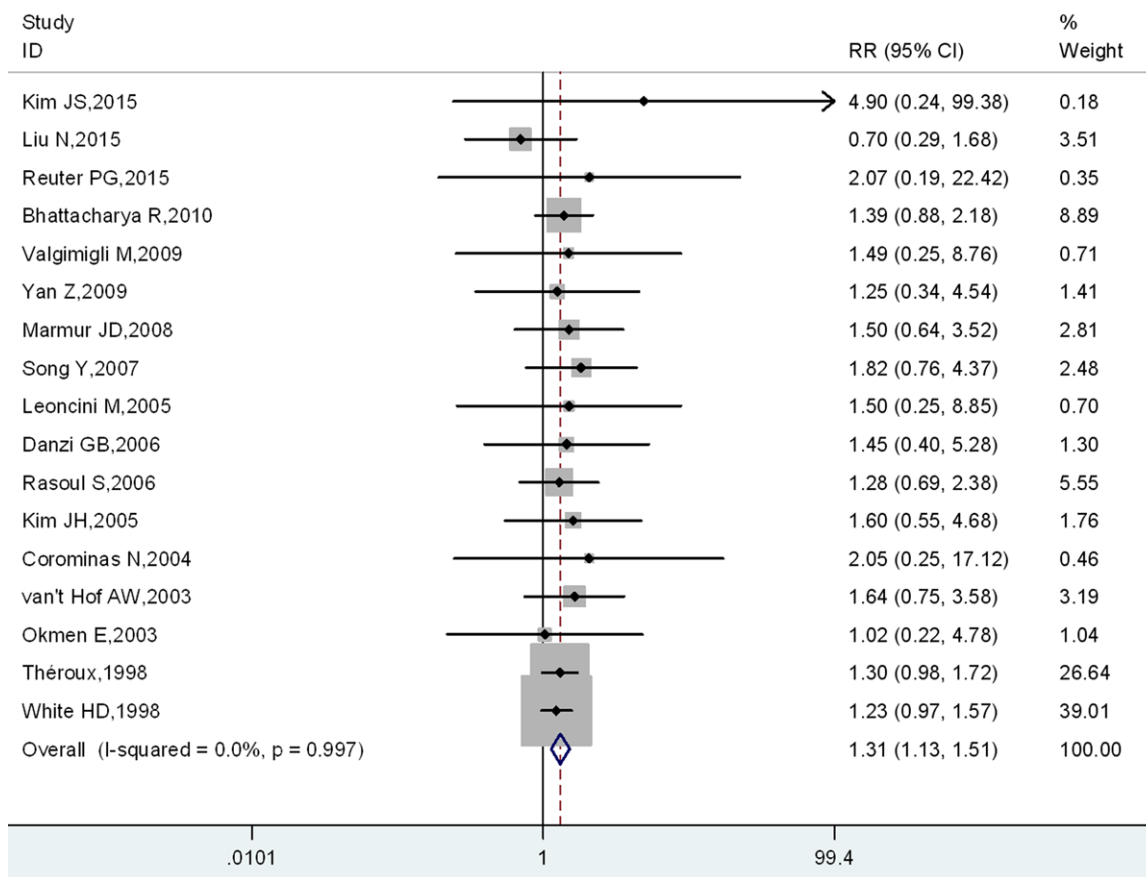


Figure 4. Forest plot of safety of tirofiban in NSTEMI ACS patients.

Major adverse cardiovascular events

As shown in **Figure 3**, tirofiban reduced the occurrence of the composite of major adverse cardiovascular events both in-hospital follow-up (RR=0.76, 95% CI: 0.61 to 0.96, P=0.018, P for heterogeneity =0.069, I²=40.8%), 30-day follow-up (RR=0.71, 95% CI: 0.59 to 0.85, P=0.000, P for heterogeneity =0.006, I²=58.2%) and ≥ 3 months of follow-up (RR=0.65, 95% CI: 0.48 to 0.86, P=0.003, P for heterogeneity =0.007, I²=75.2%), as compared with control group, and the differences were statistically significant. The result of chi-squared test showed that included trials led to apparently statistically heterogeneous results in terms of MACE rates (P for over-all heterogeneity =0.001, I²=52%). Because of the heterogeneity, we performed random effect model and subgroup analysis for meta-analysis.

Bleeding risk

Data on bleeding risk were available in 17 studies including 8485 patients. As shown in **Figure**

4, tirofiban was associated with higher bleeding risk (RR=1.31, 95% CI: 0.13 to 1.51, P=0.000, P for heterogeneity =0.997, I²=0%) in NSTEMI ACS patients compared the control group. In addition, there was no evidence of statistically heterogeneity existed in the terms of bleeding risk.

Sensitivity analysis

None of the studies influenced the results for any of the endpoints studied, such that the results would have changed significantly; the influence analysis omitting one study at a time consistently showed no difference in survival of patients treated with either strategy (**Figures 5-7**).

Publication bias

Publication bias is a common problem in meta-analysis, affects outcomes largely and difficult to control. That negative outcomes tend to be difficult to public is associated with the publication bias. The **Figures 8-10** all showed no remarkable asymmetric in the funnel plot, indi-

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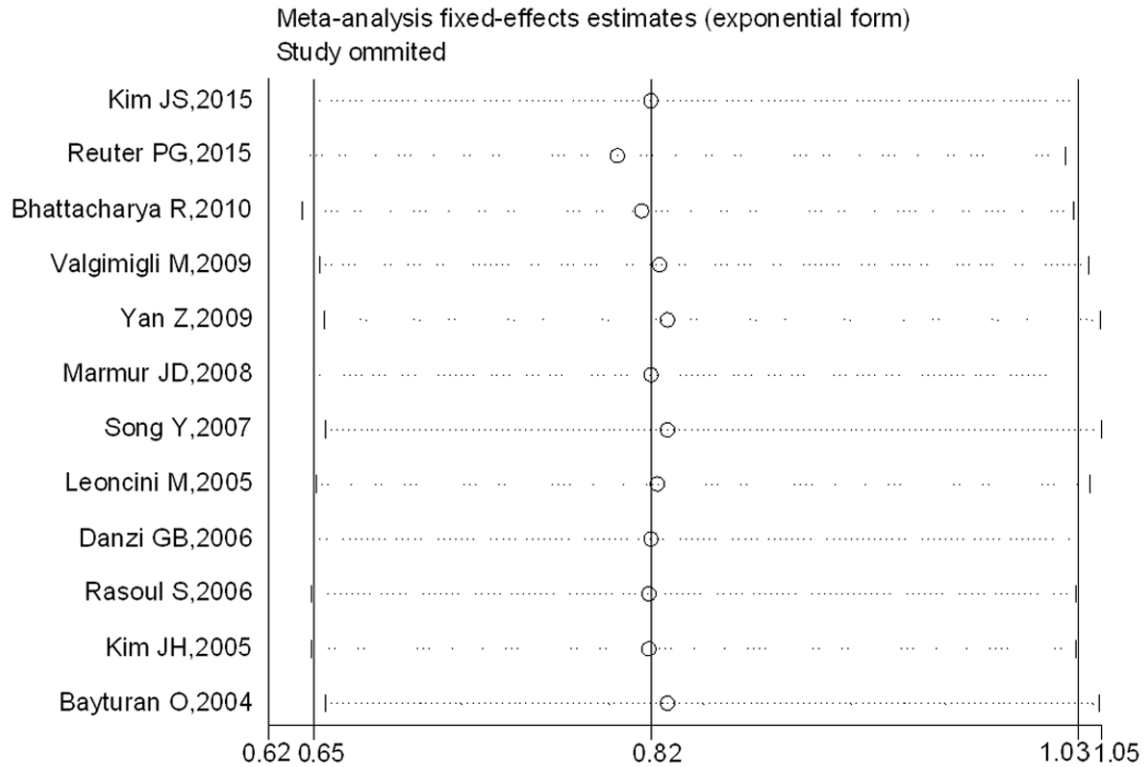


Figure 5. Sensitivity analysis of mortality of tirofiban in NSTEMI ACS patients.

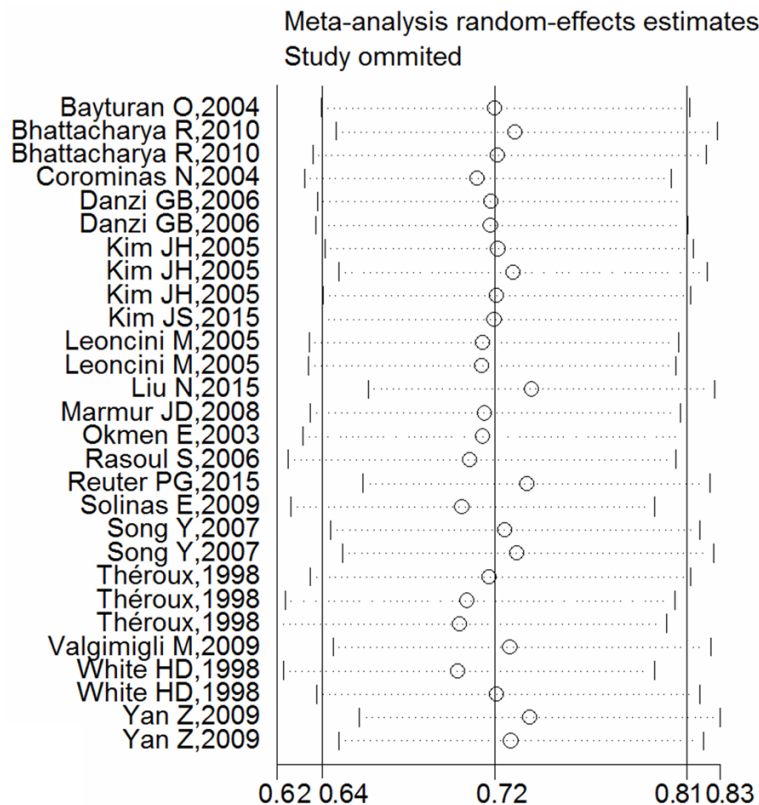


Figure 6. Sensitivity analysis of efficacy of tirofiban in NSTEMI ACS patients.

cated no remarkable publication bias in our analysis. Begg's test and Egger's test were also performed for assessing publication bias. The results of Begg's test for each endpoint were $P=0.373$, $P=0.353$, $P=0.079$, and the results of Egger's test were $P=0.764$, $P=0.063$, $P=0.585$, respectively, all showed no statistically significant publication bias, as the result of funnel plot.

Discussion

The results of the current study can be summarized as follows: 1) tirofiban did not affect the all-cause mortality compared with those treated with placebo or others ($RR=0.80$, 95% CI: 0.64 to 1.01, $P=0.066$) in NSTEMI ACS patients. 2) tirofiban statistically significantly reduced the oc-

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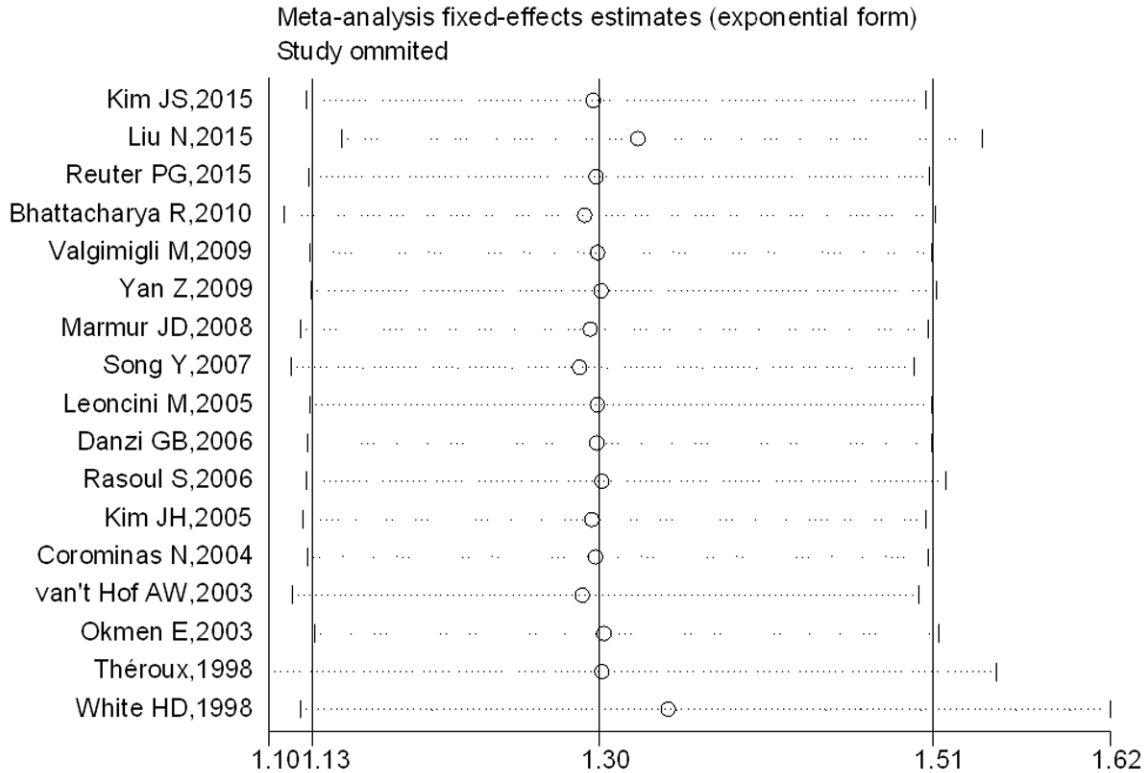


Figure 7. Sensitivity analysis of safety of tirofiban in NSTEMI ACS patients.

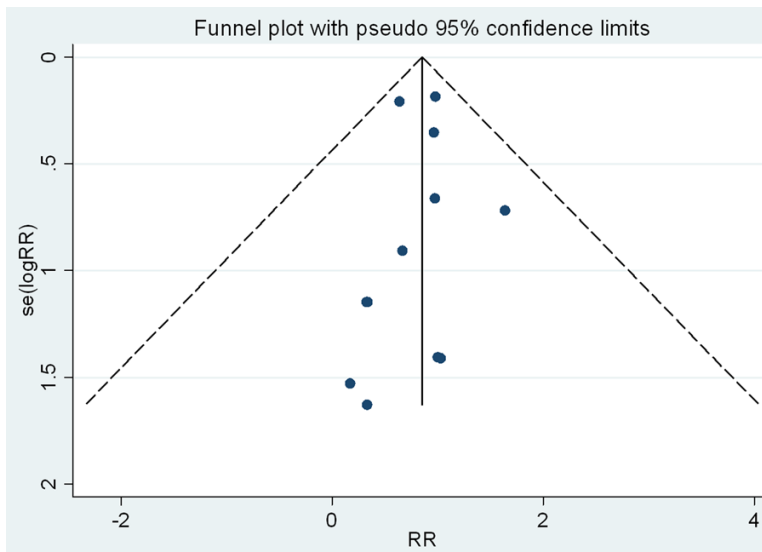


Figure 8. Funnel plot of mortality of tirofiban in NSTEMI ACS patients.

currence of the composite of major adverse cardiovascular events both in-hospital follow-up (RR=0.76, 95% CI: 0.61 to 0.96, P=0.018), 30-day follow-up (RR=0.71, 95% CI: 0.59 to 0.85, P=0.000) and ≥ 3 -month follow-up (RR=

0.65, 95% CI: 0.48 to 0.86, P=0.003), as compared with control group. 3) tirofiban tended to associated with higher bleeding risk (RR=1.31, 95% CI: 0.13 to 1.51, P=0.000) in NSTEMI ACS patients.

Formation of thrombosis mainly relies on the binding of fibrinogen and GPIIb/IIIa receptor activated on the surface of the platelet. Thus, Schwenkglenks, M. et al. [31] declared that the key to block the formation of thrombosis was to block the platelet GPIIb/IIIa receptor antagonist. Representative platelet glycoprotein IIb/IIIa inhibitors currently used are abciximab,

eptifibatide, and tirofiban. Tirofiban is a highly selective, short-acting glycoprotein platelet IIb/IIIa receptor inhibitor, it inhibits platelet aggregation by preventing the combination of fibrinogen and GPIIb/IIIa, consequently preventing

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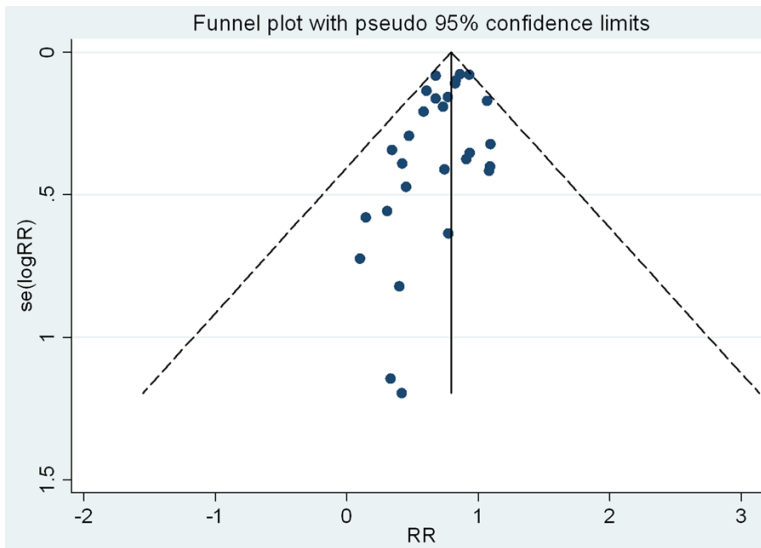


Figure 9. Funnel plot of efficacy of tirofiban in NSTEMI ACS patients.

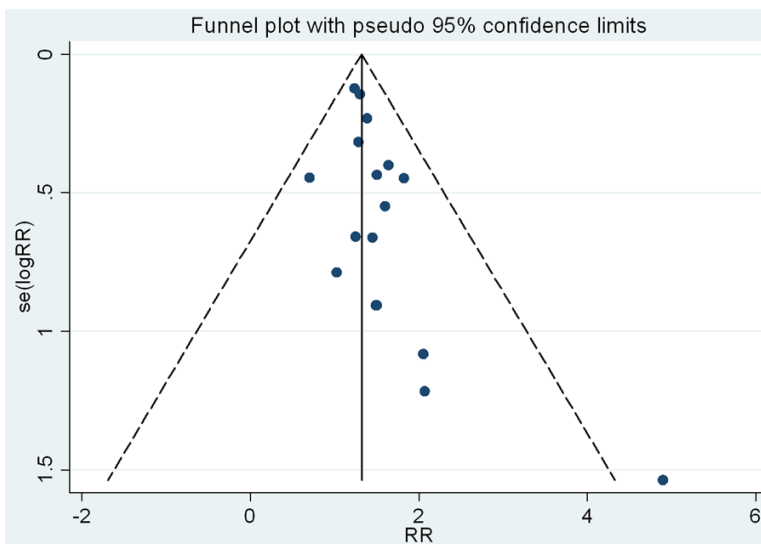


Figure 10. Funnel plot of safety of tirofiban in NSTEMI ACS patients.

acute myocardial ischemic events resulting from coronary thrombosis [32-34]. Compared to abciximab, which binds near irreversibly to the receptor, resulting in a considerably longer effect, the anti-aggregatory effects of tirofiban reverse within hours after the completion of the infusion [35, 36]. Moreover, tirofiban does not inhibit other β_3 integrins, which have been traditionally regarded as crucial targets to explain abciximab effect on microcirculation [37]. In addition, unlike eptifibatid, tirofiban shares the property of high-affinity IIb/IIIa receptor binding with abciximab [35]. However, because of the lower cost, tirofiban represents a very

attractive strategy and is more commonly used in clinical practice in Asia, compared with abciximab and eptifibatid, which are mainly used in developed country.

Our findings suggest that, treatment with tirofiban was not associated with a reduction in the odds of all-cause mortality in NSTEMI ACS patients. However, in our study, it also showed that the management of tirofiban was associated with a non-significant tendency to reduce the risk of all-cause mortality. The results of our study were consistent with the results of a PRISM-PLUS study [29], which showed that the addition of tirofiban to heparin was associated with similar all-cause death both at in-hospital ($P=0.58$), 30 days ($P=0.36$) and 6 months ($P=0.85$) of follow-up compared to heparin alone. Previous meta-analysis [38] has shown mortality at 30 days was not significantly affected by treatment with intravenously administered small molecule GPIIb/IIIa inhibitors in patients with NSTEMI ACS. However, some studies hold a contrary opinion. A meta-analysis [39] involving 66,689 patients indicated that glycoprotein IIb/IIIa blockers decreased all-cause mortality at 30 days during PCI. The difference among different studies may attribute to different GPIIb/IIIa blockers, follow-up, adjuvant therapies and so on.

The current analysis also indicated that tirofiban reduced the occurrence of the composite of death, myocardial infarction or refractory ischemia in NSTEMI ACS patients at in-hospital, 30 days, three months and six months, respectively. Certainly, similar conclusions have been drawn before. The PRISM trial [30] compared tirofiban with heparin in 3232 patients undergoing conservative treatment and PCI, found a

significant reduction in the incidence of the composite of death, myocardial infarction, or refractory ischemia at both short-term and long-term timing in the tirofiban group. In the PRISM-PLUS study [29], a greater relative risk (death, MI or refractory ischaemia) reduction at Day 7 ($P=0.004$), day 14 ($P=0.025$), day 30 ($P=0.03$) and month six ($P=0.02$) was observed among patients who were treated with tirofiban. Furthermore, Boersma et al. [40] summarized the results of six large randomized trials, involving 31402 patients with acute coronary syndromes (ACS), and found a significant reduction in the odds of death or myocardial infarction 30 days after the treatment with GPIIb/IIIa inhibitors, as compared with placebo or other control groups. However, there were several contrary conclusions. Recently, the RESTORE study group reported [4] that, though the application of tirofiban reduced the relative incidence of adverse cardiac outcomes at 2 days ($P=0.005$), and at 7 days ($P=0.02$), it tended to no significantly difference at 30 days and six months. Data from a TARGET study [5] suggested that tirofiban provided significantly less protection from major ischemic events than abciximab. In the ELISA-2 trial [23], the occurrence of MI appeared no statistically significant (57% vs. 40%, $P=0.052$) among the dual antiplatelet therapy (aspirin and clopidogrel) and triple antiplatelet therapy (aspirin, clopidogrel and tirofiban) at 30 days of follow-up. Though controversial opinions existed, our results further confirmed the efficacy of tirofiban.

Bleeding and thrombocytopenia following GPI therapy have been strongly associated with poor clinic outcomes, including death, MI, major haemorrhage, and prolonged hospitalization. Although the mechanism remains incompletely understood, possible mechanisms include presence of pre-existing or GPI exposure-dependent antibodies that increase platelet destruction, inhibition of megakaryocytes that express GPIIb/IIIa receptors, and heightened platelet microaggregation secondary to activation of the inflammatory system [41]. The findings of this analysis, that bleeding risk increased in patients treated with tirofiban, were consistent with previous reports. In the PRISM study [30], reversible thrombocytopenia occurred more frequently with tirofiban than with heparin (1.1% vs. 0.4%, $P=0.04$). Prior studies regarding the bleeding risk of tirofiban in NSTEMI ACS pa-

tients obtained inconsistent results. In the PRISM-PLUS study [29], major bleeding events were similar in patients who received heparin alone and a combination therapy (3% vs. 4%, $P=0.34$). Previously, the RESTORE study [4] showed no significant increase in thrombocytopenia or major bleeding complications in the tirofiban group versus the placebo-treated group. Similarly, in the ELISA-2 trial [23], there was no significant difference in the bleeding incidence between the dual antiplatelet therapy group and the triple antiplatelet therapy groups. The different results among different studies about bleeding complications of tirofiban may be attributed to various therapeutic in control group and being administered concomitantly with other antiplatelet drugs. In our study, tirofiban was associated with higher bleeding risk. However, no fatal bleeding was observed in included studies. Therefore, though the potential risk of bleeding complications induced by tirofiban shouldn't be ignored, it may be concluded that tirofiban is a safe anti-platelet drug.

Limitations

Several limitations must be noted when interpreting the results of this meta-analysis. First, administration of tirofiban was mainly concentrate in Asian nowadays, due to the lower costs compared with other kinds of GPIIb/IIIa such as abciximab, eptifibatide, which were used more commonly in developed counties. Thus, the current study may be more valuable in Asian. Second, in terms of MACE, substantial heterogeneity was considered to exist. However, the use of random effect model reduced the effects of heterogeneity for these dichotomous trial data. At the same time, we preformed subgroup analysis to explore resource of heterogeneity. Third, the treatment in control group was different, including placebo, ticagrelor, clopidogrel and eptifibatide, which may affected our outcomes. Forth, our analysis failed to show the risk stratification. Finally, the longest follow-up was six months, mentioned just in three studies. Therefore, further studies should be preformed to confirm long-term outcomes of tirofiban.

Conclusions

In summary, we analyzed data from 19 documents to systemically evaluate the early and later outcomes and bleeding risk in patients

with NSTEMI ACS. It could be concluded that tirofiban has a definite role in improving the outcomes of patients with non-ST segment elevation acute coronary syndromes. However, treatment with tirofiban provided no significant benefit on all-cause mortality in NSTEMI ACS patients. Furthermore, tirofiban was associated with higher bleeding risk in NSTEMI ACS patients. However, no fatal bleeding was observed in included studies. This study demonstrated that as a new generation of antiplatelet drugs, the early application of tirofiban can effectively and safely improve outcomes in NSTEMI ACS patients.

Disclosure of conflict of interest

None.

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