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Ticagrelor versus clopidogrel in East Asian patients with acute coronary syndrome: A meta-analysis

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Abstract

Objective: There exist conflicting data on the efficacy and safety of ticagrelor and clopidogrel in East Asian patients with acute coronary syndrome (ACS). We performed a meta-analysis to evaluate whether ticagrelor or clopidogrel produces better outcomes for East Asian patients with ACS. Methods: We searched for randomized controlled trials reporting associations between ticagrelor and clopidogrel in East Asian patients with acute coronary syndrome in PubMed, EMBASE, web of science and Cochrane central register of controlled trials. Results: Ten studies involving 3 715 participants were qualified for our analysis. The major adverse cardiovascular events (MACE) were significantly decreased in patients with ticagrelor treatment compared to those with clopidogrel (risk ratio [RR]: 0.61; 95% confidence interval [*CI*]: 0.38-0.98; *P* = 0.042). There was no significant difference in all-cause death (RR: 0.89; 95% CI: 0.61-1.29; *P* = 0.540), cardiovascular death (RR: 0.86; 95% CI: 0.58-1.27; *P* = 0.451), myocardial infarction (RR: 0.91; 95% CI: 0.65-1.27; *P* = 0.575) and stroke (RR: 0.77; 95% CI: 0.44-1.36; *P* = 0.372) between ticagrelor and clopidogrel. Ticagrelor was associated with a significantly higher risk of bleeding compared to clopidogrel (RR: 1.71; 95% CI: 1.37-2.13; *P* = 0.000). Conclusion: The present meta-analysis demonstrates that ticagrelor reduced the incidence of MACE in ACS patients from East Asia compared with clopidogrel. However, it increased the risk of bleeding.

Keywords

ticagrelor; clopidogrel; acute coronary syndrome; Eastern Asia; meta-analysis

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1 Introduction

Dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ receptor inhibitor is the recommended antithrombotic therapy in patients with acute coronary syndrome (ACS)[1]. Aspirin, an inhibitor of cyclooxygenase that prevents thromboxane A2 synthesis, is routinely prescribed for preventing thrombotic complications. Clopidogrel is a prodrug requiring the cytochrome P450 (CYP) enzymes for its biotransformation into an active thiol metabolite and the most widely prescribed anti-platelet drug for patients with ACS[2-3]. Ticagrelor, a direct-acting, reversibly binding $P2Y_{12}$ receptor inhibitor, is a strongly recommended agent for patients with acute coronary syndrome (ACS)[4-6]. In the PLATO trial[7], ticagrelor was shown to be superior to clopidogrel in reducing the rate of death of vascular causes, myocardial infarction, or stroke without an increase in the overall rate of major bleeding events. The PHILO trial[8], which included 801 East Asian patients with ACS, reported that the rates of primary efficacy endpoints and major bleeding were higher in ticagrelor-treated patients than clopidogrel-treated patients. The controversies of the investigation results in terms of the risk profiles of thrombophilia and bleeding for ticagrelor versus clopidogrel exist in East Asian population, likely due to different genetic backgrounds. A meta-analysis[9] enrolled 1 352 Eastern Asian patients with ACS from two randomized controlled trials (RCTs)[8-10] demonstrated ticagrelor had no advantage in regard with its antithrombotic efficiency but increased the risk of major bleeding compared to clopidogrel. Another meta-analysis included 1 552 patients from 3 RCTs[8,10,12] showed similar results. However, increasing evidence indicates that ticagrelor could provide a marginally or significantly

favorable antithrombotic efficacy in East Asian patients with ACS[13-15]. Therefore, we performed the present meta-analysis to evaluate the efficacy and safety of ticagrelor and clopidogrel in Eastern Asian patients with ACS.

2 Methods

2.1 Search strategy

This meta-analysis was conducted by following the methods as previously described in detail[16]. PubMed, EMBASE, web of science and Cochrane central register of controlled trials were independently searched by two investigators (YX Zang and DH Sun) until 1 November 2020. The following search terms or phrases were used in our study: 'clopidogrel' AND 'ticagrelor' AND ('acute coronary syndrome' OR 'unstable angina' OR 'myocardial infarction' OR 'percutaneous coronary intervention'). No language restrictions were applied.

2.2 Study selection

The studies had to fulfil the following criteria for their inclusion in our data analyses: (1) randomized controlled trials (RCT); (2) studies of East-Asian patients, which include Chinese, South Korean, Japanese and Mongolian patients; (3) the clinical trials that compared ticagrelor with clopidogrel; (4) articles with the available data for at least one of the following outcome measures: major adverse cardiovascular event (MACE) , all-cause death, cardiovascular death, stroke, bleeding, major bleeding and minor bleeding; (5) the follow-up time was ≥6 months. The exclusion criteria included the following: repetitive publications; reviews; case reports; a short-time follow-up (less than 6 months).

2.3 Data extraction

Two investigators (YX Zang and DH Sun) independently screened and assessed the titles and abstracts for eligibility using the predefined inclusion criteria. Any disagreements and discrepancies in the analysis of the results were resolved by iteration and consensus. Data included the following information: name of the first author, publication year, study period, country, study design, sample size, clinical characteristics of the study population, duration of follow-up and results of the clinical outcomes. Quality assessment of the study was performed using the Cochrane Collaboration's risk of bias tool[17], and we included all eligible RCTs regardless of their assessed quality.

2.4 Data synthesis

Analyses were performed using Stata version 12.0 statistical software (StataCorp, USA). Heterogeneity of the pooled estimates was assessed using the I^2 statistic. The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity; values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively[18-19]. All *P*-values were two-sided and less than 0.05 was considered statistically different.

3 Results

3.1 Study selection

A total of 3 861 literature citations were retrieved, including 126 potentially relevant studies as shown in Fig. 1 Of these, 126 potentially eligible articles were reviewed in full text. As a result, we included 10 articles in the meta-analysis, and the quality assessment of the study is shown in Fig. 2.

3.2 Study characteristics

Ten studies enrolled 3 715 participants matching the inclusion criteria including 1 855 participants that were designated to the ticagrelor treatment group and 1 860 participants that were designated to the clopidogrel treatment group[8,10,12-14,20-24]. The ten studies were came from countries including China, South Korea, and Japan. The baseline characteristics of the included studies and patients are shown in Table 1.

3.3 Meta-analysis

The rate of MACE (Fig. 3) with ticagrelor was dramatically lower than with clopidogrel (risk ratio [RR]: 0.61; 95% confidence interval[CI]: 0.38-0.98; $P = 0.042$). There was no significant difference in the all-cause death (RR: 0.89; 95% CI: 0.61-1.29; $P = 0.540$) (Fig. 4A), cardiovascular death (RR: 0.86; 95% CI: 0.58-1.27; $P = 0.451$) (Fig. 4B), myocardial infarction (RR: 0.91; 95% CI: 0.65-1.27; $P = 0.575$) (Fig. 4C) and stroke (RR: 0.77; 95% CI: 0.44-1.36; $P = 0.372$) (Fig. 4D) between ticagrelor treatment and clopidogrel treatment. Ticagrelor was associated with a significantly higher risk of bleeding (RR: 1.71; 95% CI: 1.37-2.13; $P = 0.000$) (Fig. 5A), which induced a significant increase in major bleeding (RR: 1.52; 95% CI: 1.11-2.09; $P = 0.010$) (Fig. 5B) and minor bleeding (RR: 1.73; 95% CI: 1.29-2.32; $P = 0.000$) (Fig. 5C), whereas clopidogrel was not.

3.4 Publication bias and sensitivity analysis

The publication bias of primary endpoint was high before sensitivity analysis or subgroup analysis（Egger's test bias $P > |t| = 0.012 < 0.05$). To explore the source of heterogeneity, the population of Chinese participants was analyzed as a subgroup,

Table 1 Baseline characteristics of included studies

References	Country	Follow-up (months)	Sample size (*n*)		Age (years)		Male (n)		Hypertension (%)		Diabetes (%)	
			Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
Goto S *et al.*, 2015[7]	China,South Korea and Japan	12	401	400	67 ± 12	66 ± 11	306	307	76.1	72.5	38.4	31.0
Kang HJ *et al.*, 2015[9]	China and South Korea	12	278	273	NA	NA	NA	NA	NA	NA	NA	NA
Xia JG *et al.*, 2015[19]	China	6	48	48	53.7 ± 10.3	54.6 ± 9.8	36	38	62.5	64.6	50	45.8
Wang HD *et al.*, 2016[11]	China	12	100	100	NA	NA	69	66	79	82	42	39
Tang XY *et al.*, 2016[20]	China	6	200	200	64.36 ± 11.41	64.18 ± 11.09	142	146	61	58	29	21
Ren Q *et al.*, 2016[21]	China	12	149	151	56 ± 9.2	55 ± 8.0	102	106	NA	NA	NA	NA
Lu YJ *et al.*, 2016[22]	China	12	95	108	59.25 ± 9.63	59.63 ± 9.88	52	60	34.7	38.9	25.3	29.6
Wu HB *et al.*, 2018[12]	China	12	124	120	58.976 ± 10.187	61.058 ± 11.600	98	94	51.6	57.5	25.8	20.8
Yang B *et al.*, 2018[13]	China	6	60	60	59.6 ± 15.7	58.7 ± 13.5	35	38	NA	NA	NA	NA
Park DW *et al.*, 2019[23]	South Korea	12	400	400	62.5 ± 11.3	62.3 ± 11.5	297	302	55.8	48.2	29.0	25.0

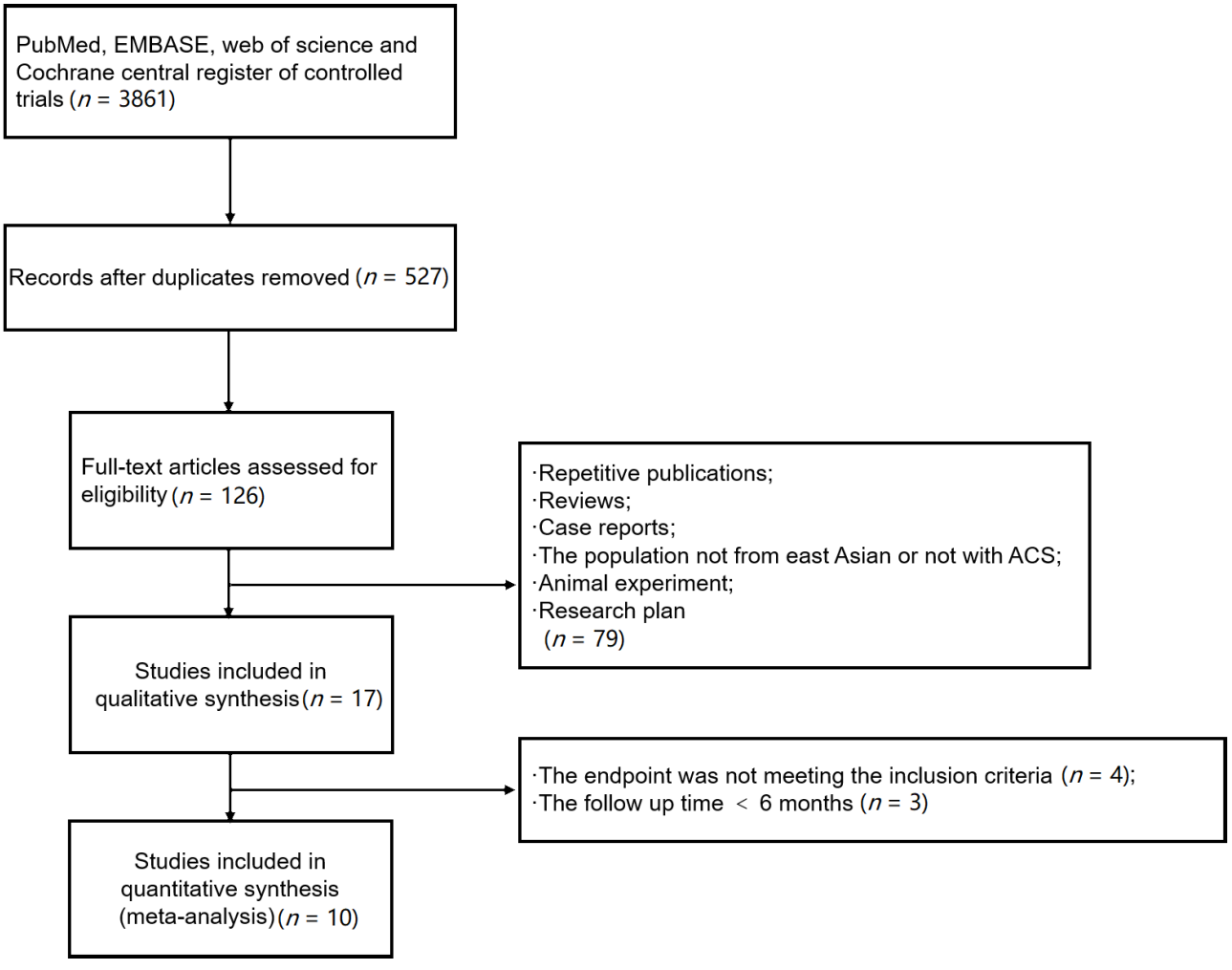

Fig. 1 Flowchart of study screening

and the publication bias was revised (Egger's test bias $P > |t| = 0.812 > 0.05$). In addition, six trials were included in the Chinese subgroup, and there was no heterogeneity ($I^2 = 0\%$, $P = 0.873$). The fixed-effects model analysis showed a significant decrease of 62% in the incidence of MACE, from 12.33% (97/787) with clopidogrel to 4.77% (37/776) with ticagrelor (*RR*: 0.38; 95% *CI*:0.26–0.54; $P < 0.001$) (Fig. 6).

4 Discussion

In the present meta-analysis, we included 3 715 participants from 10 randomized controlled trials for the evaluation of the efficacy and safety of ticagrelor and clopidogrel in Eastern Asian patients with ACS. The results revealed three important findings. First, the MACE was dramatically decreased in patients treated with ticagrelor compared to those with clopidogrel. Second, there was no significant difference in the all-cause death, cardiovascular death, myocardial infarction and stroke between the two drug groups. Third, compared with clopidogrel, ticagrelor showed a remarkably higher risk of bleeding.

Ticagrelor is a direct-acting, reversibly binding $P2Y_{12}$ receptor antagonist for orally administration, which inhibits adenosine diphosphate–induced platelet aggregation. The PLATO trial, an international, multicenter, randomized, double-blind trial that enrolled 18 624 ACS patients, showed that ticagrelor significantly reduced the incidence of MACE (a composite of death from vascular causes, myocardial infarction or stroke) (569 [event rate at 360 days 9.0%] *vs* 668 [10.7%], hazard ratio 0.84, 95% CI 0.75–0.94; $P = 0.0025$) [25]. However, two meta-analyses[9,11] found that ticagrelor and clopidogrel displayed similar efficacies in ACS patients from East Asia. The present meta-analysis

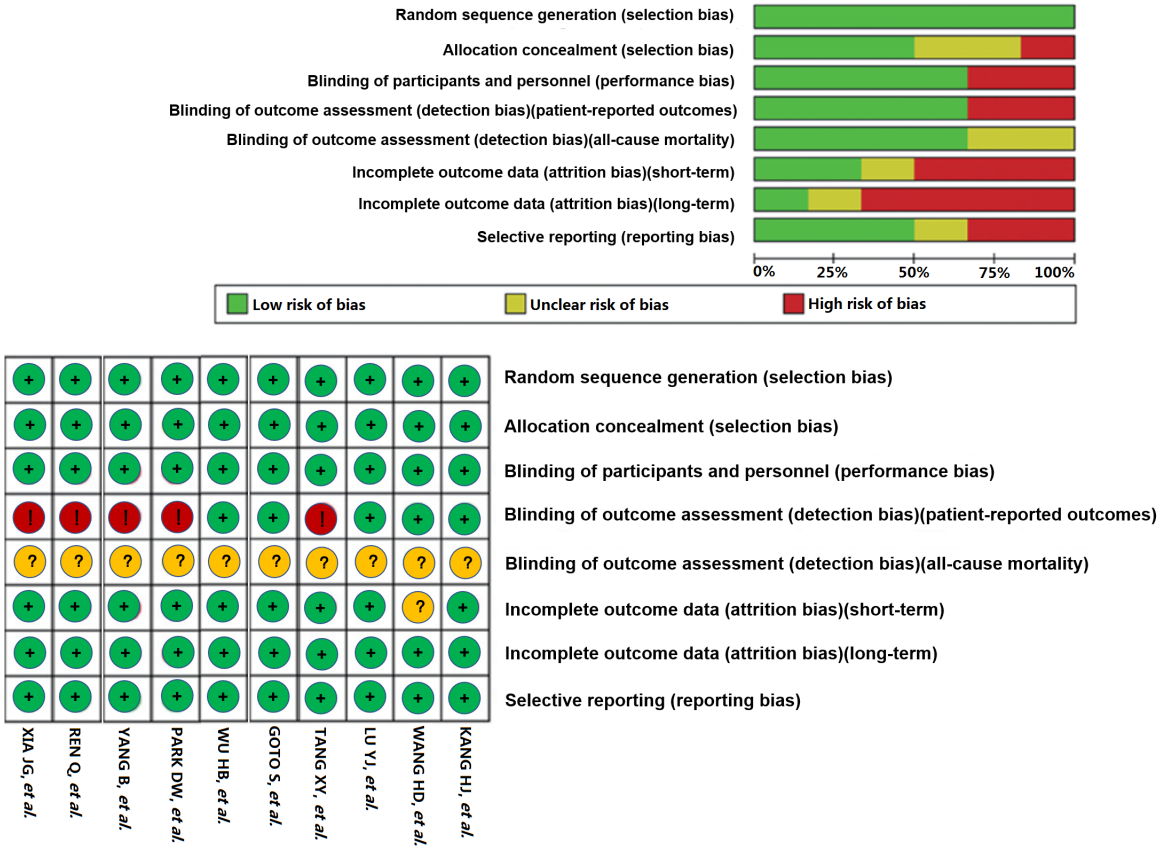

Fig. 2 The quality assessment of the study

showed that the MACE was dramatically decreased in patients treated with ticagrelor compared to those with clopidogrel. Moreover, the present meta-analysis enrolled a greater number of trials and more Eastern Asian patients with ACS and provided more convincing results.

In the setting of ACS, the safety profile of $P2Y_{12}$ inhibitors, primarily the risk of major bleeding, is a concern among clinicians and patients. The PLATO trial found there was no difference between clopidogrel and ticagrelor in the rates of total major bleeding (691 [11.6%] *vs* 689 [11.5%], 0.99 [0.89-1.10]; *P* = 0.880 3). A recent SPACE-AA study[26] which enrolled the patients from French national healthcare database demonstrated that ticagrelor had a significantly smaller risk of major bleeding than clopidogrel (163 [1.8%] *vs* 170 [1.8%], 1.02 [0.82-1.26]). However, our meta-analysis demonstrated that ticagrelor was associated with a higher risk of major bleeding relative to clopidogrel in East Asian patients with ACS. This result is essentially the same as that reported by two published meta-analyses[9,11]. A recent study carried out in New Zealand involving patients with acute myocardial infarction showed that the rate of minor bleeding one year post treatment was not significantly different in ticagrelor-treated patients from that in clopidogrel-treated patients (11.9% *vs* 11.2%, *P* = 0.73)[27]. Our meta-analysis focused on East-Asian patients and found that ticagrelor had a remarkably higher risk in the minor bleeding than clopidogrel (RR: 1.73; 95%CI: 1.29-2.32; *P* = 0.000). This discrepancy could be explained by the racial variations in the bleeding risk. It was reported that the exposure rate to active metabolites was higher (nearly 20–30%) and pharmacodynamic reaction was stronger in Asian patients than in Caucasian following treatment with the same doses of $P2Y_{12}$ inhibitors[28]. In addition, the exposures to ticagrelor and its active metabolite (AR-C124910XX) in Japanese volunteers tended to be 40% and 48% higher, respectively, than the white subjects, and even after being adjusted for body mass, the rates remained 14%

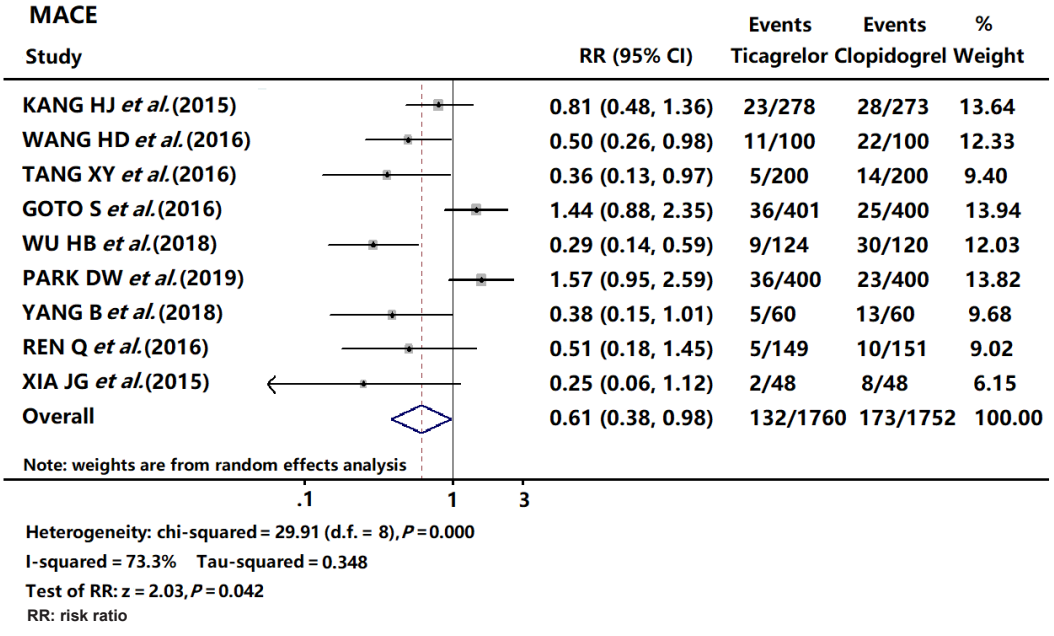

Fig. 3 Forest plots of major adverse cardiovascular events (MACE) between ticagrelor and clopidogrel

and 20% higher respectively[29]. Consistently, Li *et al*.[30] reported that compared with Caucasian counterparts, Chinese subjects tended to have approximately 40% higher concentrations of ticagrelor and AR-C124910XX Cmax and area under the plasma concentration-time curve of ticagrelor (90 mg twice daily). These studies suggested that East Asians are more susceptible to bleeding when treated with the standard-dose ticagrelor. Thus, to formulate appropriate dosages of anti-platelet agents to yield sufficient therapeutic efficacy and to minimize the risk of bleeding is crucial for ensuring successful and safe treatment of Eastern Asian patients with ACS.

In our previous study, we found that low-dose of ticagrelor elicited a greater platelet inhibitory effect than clopidogrel in Chinese patients with coronary artery disease (CAD)[31-34]. In the PEGASUS-TIMI 54 trial[35], ticagrelor at either 60 mg or 90 mg twice daily reduced the risk of cardiovascular death, myocardial infarction, or stroke in patients with myocardial infarction. These findings suggested an ideal balance in maintaining an adequate anti-platelet efficacy and minimizing the risk of adverse events is crucial to the successful treatment of CAD (in both East Asian and western patients). However, studies on comparing low doses with standard doses of ticagrelor to evaluate the efficacy and safety in patients with CAD are still rather sparse. Larger-scale, well-designed studies with different doses of ticagrelor in patients with CAD are urgently needed.

5 Limitation

The limitations of this meta-analysis should be noted. First, the small number of enrolled patients from three Asian countries is the major limitation of the present analysis. Second, we only included PubMed, EMBASE, web of science and Cochrane central register of controlled trials for our search, and studies from other databases may have been missed out. Therefore, larger-scale studies that evaluate the efficacy and safety of ticagrelor and clopidogrel in Eastern Asian patients are warranted.

6 Conclusion

In conclusion, this meta-analysis demonstrated that ticagrelor yields a better efficacy in reducing the incidence of MACE in ACS patients from East Asia compared with clopidogrel. However, ticagrelor increases the risk of bleeding.

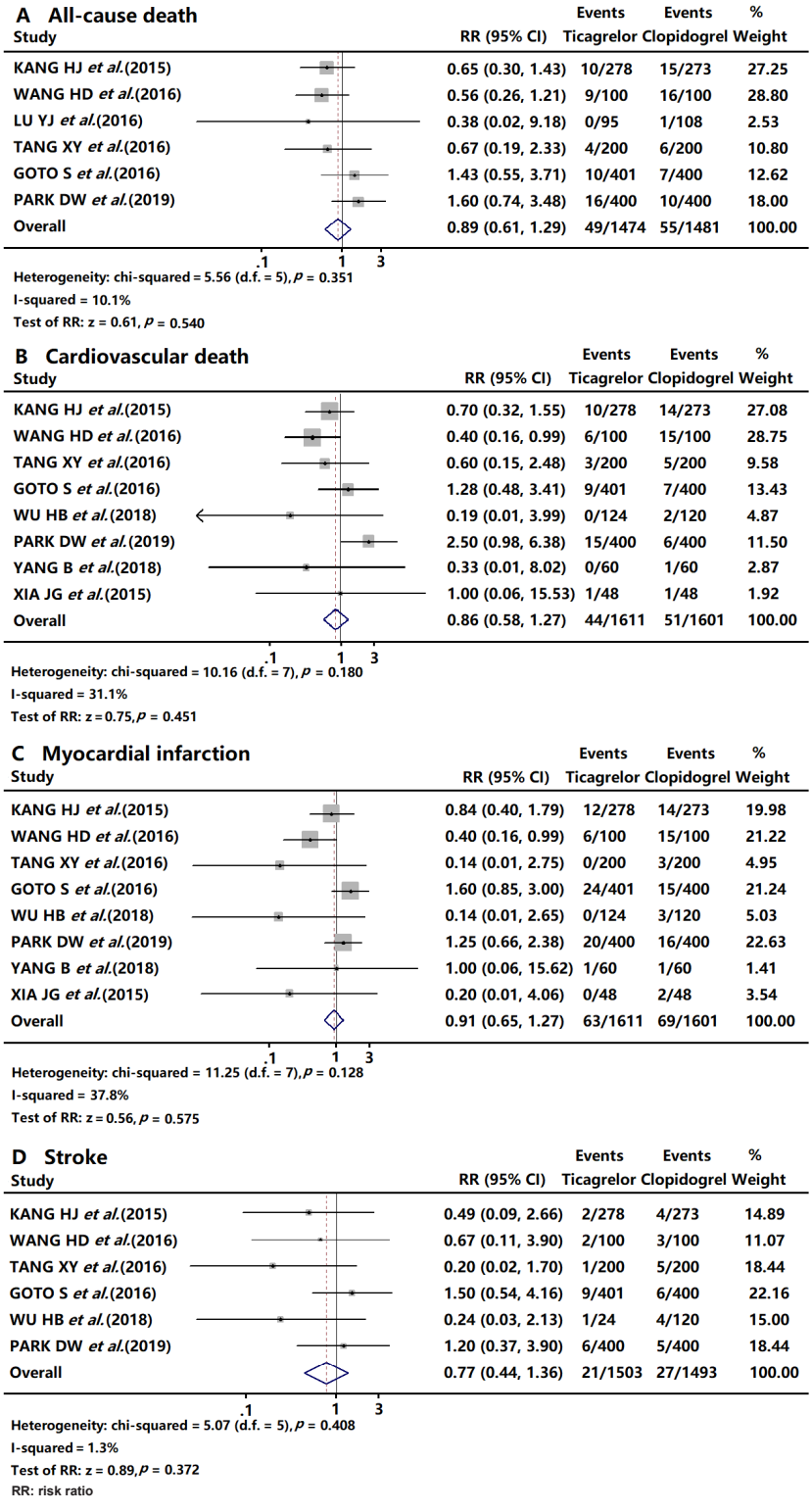

Fig. 4 Forest plots of A (All-cause death), B (Cardiovascular death), C (myocardial infarction), D (Stroke) between ticagrelor and clopidogrel

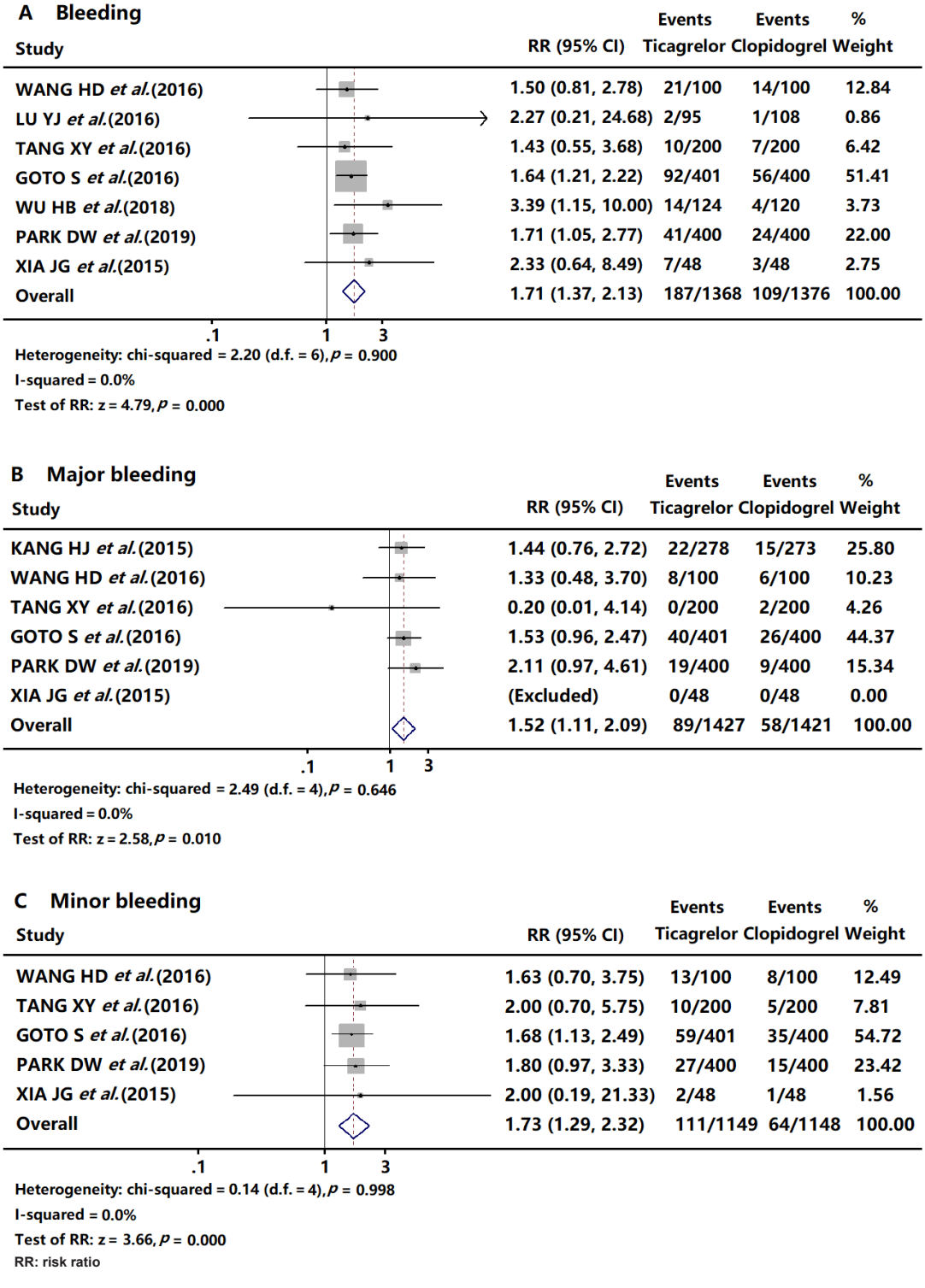

Fig. 5 Forest plots of A (Bleeding), B (Major bleeding), C (Minor bleeding) between ticagrelor and clopidogrel

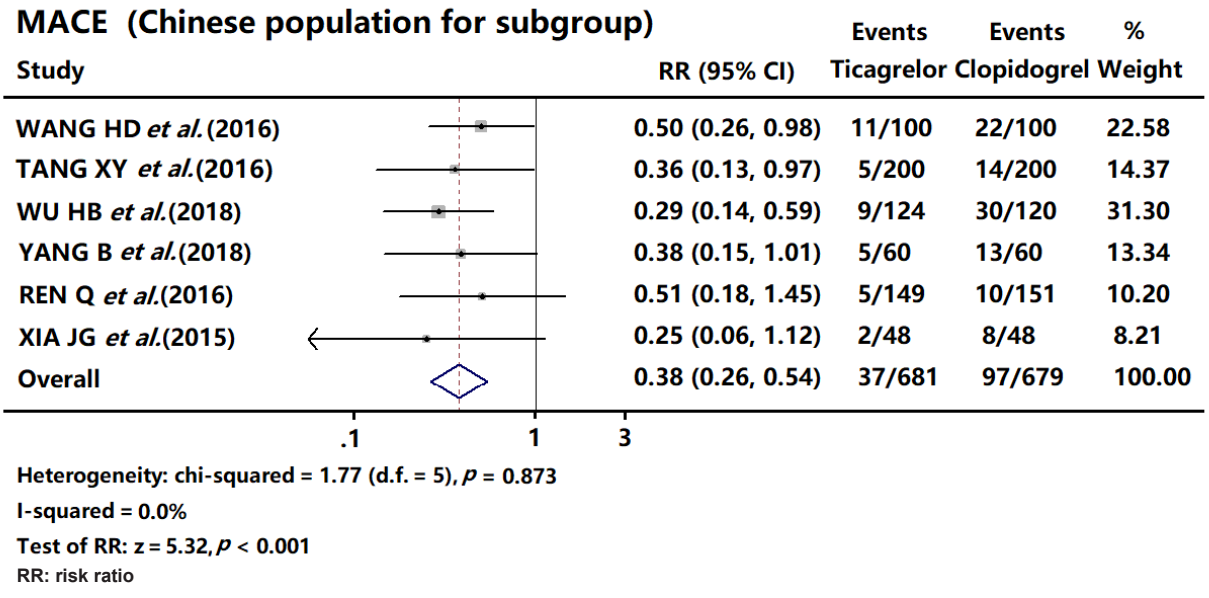

Fig. 6 Publication bias and sensitivity analysis. Forest plots of MACE in the Chinese population

Ethical approval and informed consent

This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Harbin Medical University, and all participants signed informed consent form.

Author contributions

Yanxiang Zang and Danghui Sun designed the study and analyzed data. Meijiao He wrote the draft of the manuscript. All authors contributed to the interpretation of data, critical revision of the manuscript, and provided final approval of the submitted and published version.

Conflicts of interests

Yue Li is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and his research groups.

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