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Efficacy and safety of low dose ticagrelor in patients with acute coronary syndrome: a systematic review and meta-analysis

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ABSTRACT

Our aim was to examine clinical trials, provide guidance to practitioners and estimate the efficacy and safety of two agents by comparing low dose ticagrelor with standard dose clopidogrel in patients with acute coronary syndrome. We systematically looked through Pubmed, Embase, the Cochrane Library, Wanfang data and CNKI for trials comparing low dose ticagrelor with standard dose clopidogrel for the treatment of patients with ACS since the database was created. The primary endpoint for efficacy was the rate of major adverse cardiac events (MACEs). The primary endpoint for safety was the rate of major bleeding events. We also evaluated platelet function between low dose ticagrelor and standard dose clopidogrel in ACS patients. From 6744 articles, 16 studies including 1629 patients met the inclusion criteria. In contrast with standard dose clopidogrel, low dose ticagrelor significantly reduced MACEs (OR 0.39, 95% CI 0.26, 0.58) and the difference was statistically significant ($p < 0.01$). No difference was noted for major bleeding events (OR 1.16, 95% CI 0.43, 3.08) between the two agents ($p = 0.77$). In addition, low dose ticagrelor showed lower platelet aggregation rate than clopidogrel (standardised mean difference (SMD) -0.68 , 95% CI -0.83 to 0.53) ($p < 0.01$). Platelet reaction units for low dose ticagrelor were much lower than those for standard dose clopidogrel (SMD -2.46 , 95% CI -2.85 to -2.07) ($p < 0.01$). In comparison with standard dose clopidogrel, low dose ticagrelor significantly lowered the incidence of MACEs, improved left ventricular ejection fraction, decreased left ventricular end diastolic dimension and did not expand the risk of major bleeding events or minor or minimal bleeding events in ACS patients with a considerable safety and efficacy profile. In addition, low dose ticagrelor was associated with dramatically lower platelet aggregation compared with standard dose clopidogrel.

INTRODUCTION

Acute coronary syndrome (ACS) is a common cardiovascular disease caused by coronary atherosclerotic stenosis or obstruction, which leads to myocardial ischaemia, hypoxia or myocardial necrosis, threatening human health. It has a high incidence and mortality rate, which seriously affects lifestyle and the prognosis of patients.^{1 2} Dual antiplatelet therapy (DAPT) as an effective treatment for ACS patients can reduce platelet reactivity and prevent ischaemic events.^{3–5}

The current guidelines recommend ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily with aspirin in ACS patients for DAPT usage. These recommendations are founded on large, multicentre, double blind, randomised clinical trials. Compared with clopidogrel, the higher titre P2Y₁₂ inhibitor ticagrelor reduces the incidence of cardiovascular recurrent events in ACS patients after percutaneous coronary intervention (PCI), but in clinical practice, especially in Asia, the risk of bleeding is increased, limiting drug use.⁶

In a controversial study, routine dose ticagrelor was found to increase the risk of major and minor bleeding in ACS patients compared with clopidogrel.⁷ So far, few studies have documented the efficacy of low dose of ticagrelor in ACS patients. Therefore, we assessed the efficacy and safety of low dose ticagrelor compared with standard dose clopidogrel in ACS patients by meta-analysis.

METHODS

Data extract and search protocol

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁸ The protocol of this meta-analysis was registered in advance by the International Prospective Register of Systematic Reviews (PROSPERO, identification No CRD42020171621). Our group found relevant publications comparing low dose ticagrelor with standard dose clopidogrel for the treatment of patients with ACS, with no language restrictions, in the databases Pubmed, Embase, Cochrane Library, Wanfang data and CNKI. The following search terms or phrases were used: ‘ticagrelor, clopidogrel’. The terms ‘coronary artery disease’ and ‘acute coronary syndrome’ were also included in the search strategy (see online supplementary data S1 for full list). In addition, we also hand searched the official websites of highly qualified journals (eg, *New England Journal of Medicine*, *The Lancet*, *Journal of the Circulation* and American College of Cardiology) for relevant documents. We took all potentially eligible studies for review into account, irrespective of country or language.

Inclusion and exclusion criteria

Inclusion criteria

1. Clinical trials that compared low dose ticagrelor with standard dose clopidogrel in ACS patients with all forms.

- The observation group of the intervention was low dose ticagrelor and the control group was standard dose clopidogrel. The rest of the intervention measures were consistent and the treatment course was not limited.
- The studies were eligible and provided accurate and complete statistical data, including at least one outcome: major adverse cardiac event (MACEs), major bleeding events, minor or minimal bleeding events, non-bleeding adverse events (AEs), left ventricular ejection fraction (LVEF), left ventricular end diastolic dimension (LVDD), platelet aggregation rate (PAGr) and platelet reaction unit (PRU) values.

Exclusion criteria

- The research did not compare low dose ticagrelor with standard dose clopidogrel.
- The data were unsuitable to be used in this meta-analysis.
- Review articles, clinical trials, case reports and discussion papers.

Primary indices assessing efficacy

- ▶ MACEs: cardiovascular death, myocardial infarction and stroke.⁹
- ▶ LVEF.
- ▶ LVDD.

Secondary indices assessing safety

- ▶ Major bleeding events: fatal bleeding, intrapericardial bleeding with cardiac tamponade, intracranial bleeding, hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, clinically overt or apparent bleeding associated with a decrease in haemoglobin of >5 g/dL, or transfusion of C4 units of whole blood or packed red blood cells for bleeding.⁹⁻¹⁰
- ▶ Minor bleeding events: medical intervention needed to stop or treat the bleeding when necessary.⁹⁻¹¹
- ▶ Minimal bleeding events: medical intervention is not needed or no treatment is required for the bleeding events.⁹⁻¹¹
- ▶ Non-bleeding adverse events: dyspnoea, bradycardia, diarrhoea, ventricular tachycardia and drug discontinuation, but particularly dyspnoea.⁹⁻¹¹

Outcomes assessing platelet reactivity

- ▶ Platelet aggregation rate (PAGr) using traditional light transmission aggregometry to assess platelet aggregation.⁹⁻¹²
- ▶ Platelet reaction units (PRU) using the VerifyNow assay to measure platelet aggregation.⁹⁻¹²

Data extraction

Two independent researchers reviewed the study titles and abstracts, and potentially relevant articles satisfying the inclusion criteria were reviewed in detail. Trials selected for data extraction and detailed analysis were performed by two researchers. Disagreements were resolved by a third researcher.

The bias risk was evaluated according to the modified Jadad scale. A score of 2 means a low risk of bias, a score of 1 implies unclear bias risk or medium risk, and a score of 0 represents a high risk of bias. Scores were given to each of the four components.

Method of meta-analysis and evaluation of heterogeneity reported bias

For the dichotomous outcome variables (including MACEs, major bleeding events, minimal bleeding events and non-

bleeding adverse events) the Peto method was used to weight the statistics. We found that it showed better statistical properties when there were few events or the data were sparse, regardless of the low event rates or small study size. For continuous outcome variables (including LVEF, LVDD, PAGr and PRU) the inverse variance method was used to weight the statistics.¹³

Heterogeneity was evaluated by two statistical techniques: the Cochran Q statistic test and the I^2 statistic test. A p value <0.05 or $I^2 >50%$ indicated high heterogeneity. Also, a narrower CI means the reliability of the estimation of the population mean from the sample mean was better. The point estimate around 50% also indicates better reliability of the estimation of the population mean from the sample mean. A fixed effects model was used to combine the data when $I^2 \leq 50%$, and a random effects model was performed when I^2 was >50%. In the meta-analysis, a fixed effects model was used to combine the data.

In the meta-analyses for each outcome, a funnel plot was constructed with each trial's effect size and SE, to assess publication bias. Begg's test and Egger's test were used to evaluate funnel plot asymmetry, and significant publication bias was defined as $p < 0.1$. We used the trim-and-fill computation to evaluate the effect of publication bias on the interpretation of the results, and calculated odds ratios (OR) and 95% CIs with Stata (V.11.0).

RESULTS

Searched outcomes

We researched the literature on low dose ticagrelor before starting this meta-analysis. We considered ticagrelor 90 mg once a day, 45 mg twice a day and 60 mg twice a day as low dose ticagrelor, based on extracted data from five studies.¹⁴⁻¹⁸ A total of 6744 articles were selected through database searching. We assessed the abstracts of these articles and 62 potentially relevant articles were reviewed in detail. Consequently, 16 publications underwent qualitative and quantitative analysis (figure 1).

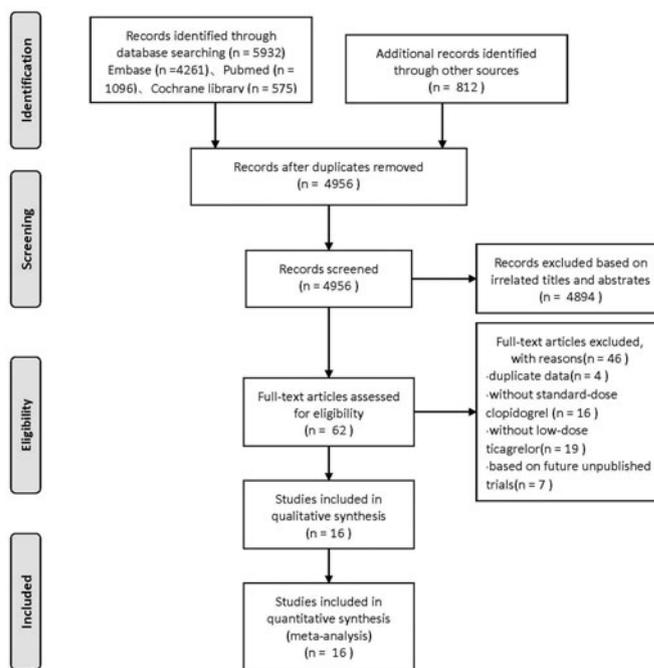


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the study selection process.

Table 1 General features of the studies included in the analysis

First author (year) ^{ref}	Country	Study design	Patients (n)	Age (years)	Men (%) (Clo/Tic)	DM (%) (Clo/Tic)	HTN (%) (Clo/Tic)	HLD (%) (Clo/Tic)	Smokers (%) (Clo/Tic)	Follow-up	Patients	Interventions
Li (2015) ³	China	RCT	157	62.9	64.6/60.3	100/100	40/37.5	35/30	/	6 months	ACS	Ticagrelor 90 mg once daily
Chen (2016) ⁴	China	RCT	98	63.0	57.1/61.2	100/100	/	/	/	6 months	ACS	Ticagrelor 90 mg once daily
Xu (2016) ⁵	China	RCT	80	61.1	60/62.5	37.5/32.5	38.8/32.7	34.7/38.8	53.1/57.1	6 months	ACS	Ticagrelor 45 mg twice daily
Jin <i>et al</i> (2017) ⁶	China	RCT	112	59.8	53.6/46.4	/	/	/	/	12 months	ACS	Ticagrelor 90 mg once daily
Hao <i>et al</i> (2017) ⁷	China	RCT	203	65.5	68.9/70.8	54.4/53.1	/	/	/	12 months	ACS	Ticagrelor 90 mg once daily
Choi <i>et al</i> (2017) ⁹	Korea	RCT	62	62.4	/	25/20/18	60/55/41	5/10/18	30/55/23	28 days	ACS	Ticagrelor 45 mg twice daily or ticagrelor 90 mg once daily
Park <i>et al</i> (2018) ¹¹	Korea	RCT	43	/	/	/	/	/	/	30 days	ACS	Ticagrelor 60 mg twice daily
Dimitrios <i>et al</i> (2017) ¹²	Greece	RCT	20	58.5	/	70	90	/	35	14 days	ACS	Ticagrelor 60 mg twice daily
Sun (2017) ¹⁹	China	RCT	78	56.4	66.7/64.1	/	/	/	/	30 days	ACS	Ticagrelor 90 mg once daily
Hu (2017) ²⁰	China	RCT	52	69.6	/	42.3/34.6	/	/	/	3 months	ACS	Ticagrelor 45 mg twice daily
Liao (2017) ²¹	China	RCT	160	63.9	55/53.8	/	/	/	/	3 months	ACS	Ticagrelor 90 mg once daily
Meng <i>et al</i> (2017) ²²	China	RCT	134	65.3	53.9/51.9	/	/	/	/	1 month	ACS	Ticagrelor 45 mg twice daily
Song <i>et al</i> (2017) ²³	China	RCT	95	62.1	60.6/67.7	30.3/29	32	34.2/38.5	53.2/56.4	6 months	ACS	Ticagrelor 45 mg twice daily
Liu (2017) ²⁴	China	RCT	76	49.9	57.9/52.6	/	51.5/45.2	27.3/25.8	51.5/46.8	3 months	ACS	Ticagrelor 90 mg once daily
Li (2015) ²⁵	China	RCT	219	62.3	72.8/72.1	39.8/44.7	/	36.1/37.8	43.6/46	12 months	ACS	Ticagrelor 45 mg twice daily
Xue <i>et al</i> (2016) ²⁶	China	RCT	40	60.2	60/70	/	35/60	50/30	25/50	5 days	ACS	Ticagrelor 45 mg twice daily

/, not reported; ACS, acute coronary syndrome; Clo/Tic, clopidogrel/ticagrelor; DM, diabetes mellitus; HLD, hyperlipidaemia; HTN, hypertension; RCT, randomised controlled trial.

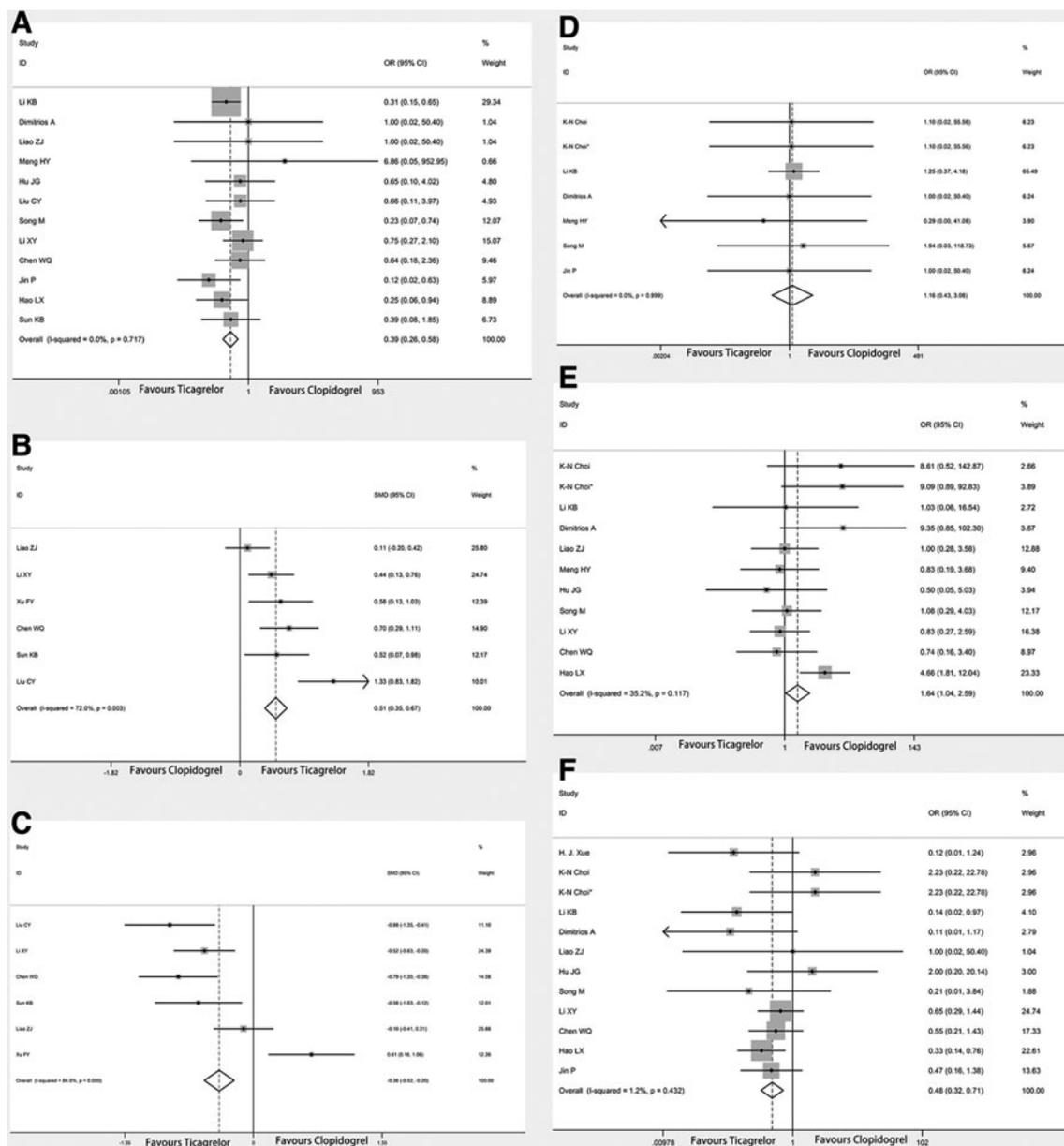


Figure 2 Forest plot showing efficacy (primary outcomes) and safety (secondary outcomes) observed between low dose ticagrelor and standard dose clopidogrel, including (A) MACEs, (B) LVEF, (C) LVDD, (D) major bleeding events, (E) minor or minimal bleeding events and (F) AEs. MACEs, major adverse cardiac events; LVDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; AEs, non-bleeding adverse events.

Description of studies

Sixteen studies with 1629 patients, 756 patients treated with low dose ticagrelor and 873 patients treated with standard dose clopidogrel, were recruited in this analysis.^{3–7 9 11 12 19–25} Some differences existed in the included studies regarding study design and patient characteristics. All studies were randomised controlled trials and published in 2015–2018. Patients were from territories worldwide, but especially from Korea, Greece and China. However, the doses of ticagrelor used in these studies were different, including 484 patients who received ticagrelor 90 mg once a day,^{3 4 6 7 9 19 21 24} 240 patients who received ticagrelor 45 mg twice a day^{5 9 20 22 23 25 26} and 32 patients who received ticagrelor 60 mg twice a day.^{11 12} All participants received aspirin 75–125 mg and did not receive other antithrombotic agents. However, non-antithrombotic agents were used, including beta receptor antagonists, statins and angiotensin converting enzyme inhibitors, among others. Individual study

characteristics, patient characteristics and inclusion/exclusion criteria of the included studies are shown in [table 1](#).

Primary outcomes (outcomes representing efficacy)

Compared with standard dose clopidogrel, low dose ticagrelor significantly reduced MACEs (OR 0.39, 95% CI 0.26, 0.58),^{3 4 6 7 12 19–25} increased LVEF (standardised mean difference (SMD) 0.51, 95% CI 0.35, 1.82)^{3–5 19 21 24} and decreased LVDD (SMD -0.36 , 95% CI -0.52 to -0.20),^{3 4 19 24} and the differences were significant ($p < 0.01$) ([figure 2](#)). However, the I^2 value for studies assessing changes in LVEF was 72.0% in ACS patients, indicating significant heterogeneity across the studies. Subgrouping according to age, region, follow-up duration and dose of ticagrelor had no pronounced effect on the I^2 values, but I^2 was reduced to 37.5% after excluding data for one study with higher weightings ($>50\%$). Similarly, the I^2 value for studies assessing changes in LVDD was 84.0%, and I^2 was reduced to

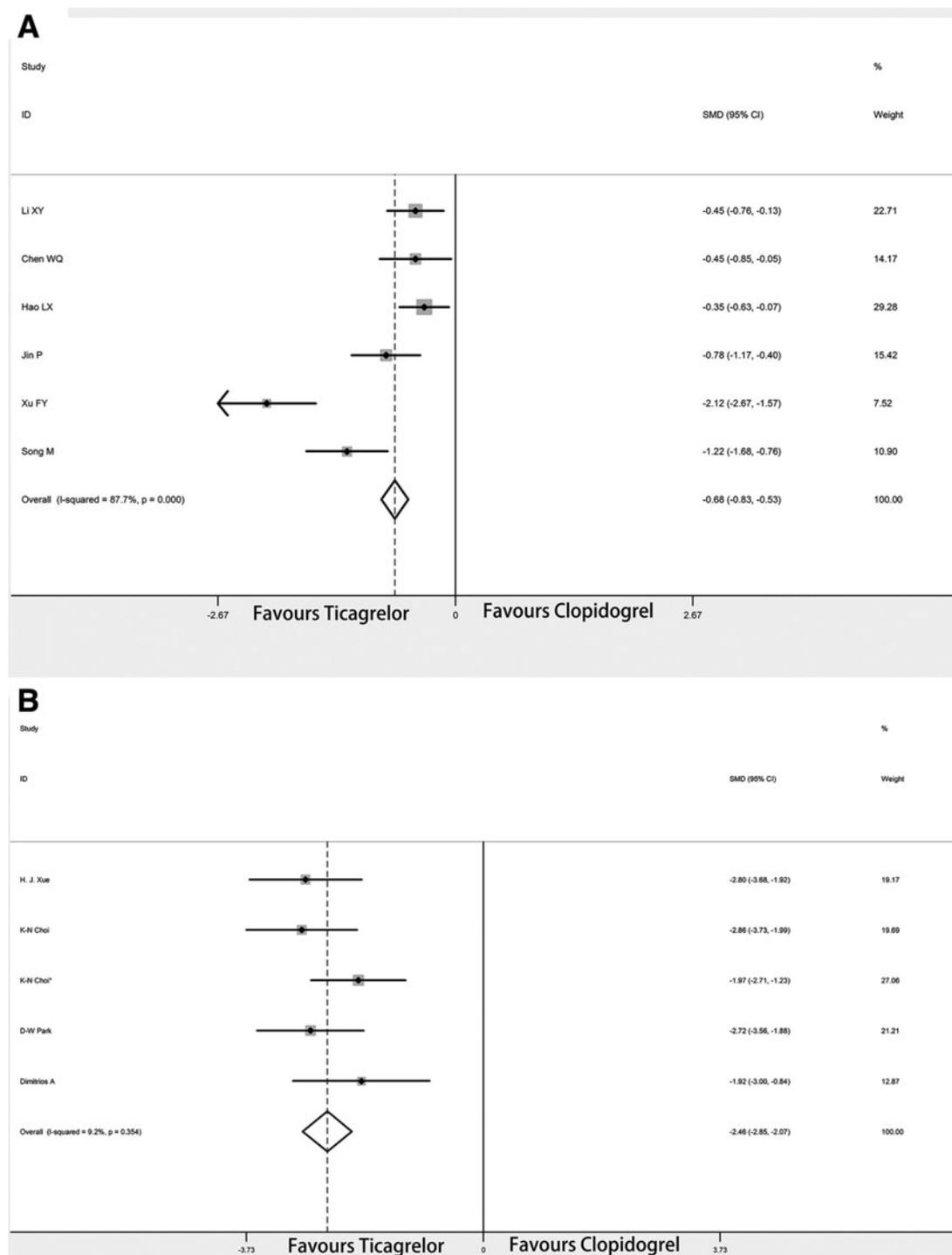


Figure 3 Forest plot showing platelet reactivity observed between low dose ticagrelor and standard dose clopidogrel, including (A) platelet aggregation rate and (B) P2Y12 reaction units.

0 after excluding data from two studies with higher weightings (>50%).

Secondary outcomes (outcomes representing safety)

The I^2 value for studies assessing safety outcomes was $\leq 50\%$ in ACS patients, and a fixed effects model was used to combine the data. Major bleeding events were not significantly different with low dose ticagrelor versus standard dose clopidogrel (OR 1.16, 95% CI 0.43, 3.08; $p=0.77$).^{6 9 12 22 23 25} Compared with standard dose clopidogrel, low dose ticagrelor significantly decreased the incidence of

minor or minimal bleeding events (OR 1.64, 95% CI 1.06, 2.59; $p=0.04$)^{3 4 6 7 9 12 20–23 25} and AEs (OR 0.48, 95% CI 0.32, 0.71; $p<0.01$)^{3 4 7 9 12 20 21 23 25 26} (figure 2).

Outcomes representing platelet reactivity

Low dose ticagrelor showed lower PAgr than clopidogrel (SMD -0.68 , 95% CI -0.83 to -0.53 ; $p<0.01$).^{3 4 6 7 23} PRU values for low dose ticagrelor were also lower than those for standard dose clopidogrel (SMD -2.46 , 95% CI -2.85 to -2.07 ; $p<0.01$) (figure 3).^{9 11 12 26}

Table 2 Univariate meta-regression for efficacy and safety of low dose ticagrelor in patients with acute coronary syndrome

Covariate	MACE	LVEF	LVDD	Major bleeding events	Minor or minimal bleeding events	Non-bleeding adverse events	PAGr	PRU
Average age	1.01 (0.47, 2.18)* (p=0.97)	1.60 (0.66, 3.84) R ² =29.05%, (p=0.21)	0.59 (0.16, 2.18) R ² =4.94%, (p=0.33)	0.91 (0.14, 5.94)* (p=0.91)	2.34 (0.80, 6.81) R ² =100.00%, (p=0.11)	0.75 (0.39, 1.45)* (p=0.36)	1.23 (0.42, 3.58) R ² =-20.93%, (p=0.62)	1.46 (0.46, 4.62) R ² =1.06%, (p=0.37)
Region	2.48 (0.25, 246.59)* (p=0.67)	NR	NR	0.91 (0.14, 6.09)* (p=0.91)	2.79 (0.77, 10.10) R ² =15.01%, (p=0.10)	1.90 (0.70, 5.15)* (p=0.18)	NR	1.09 (0.42, 2.79) R ² =-192.02%, (p=0.80)
Follow-up	0.58 (0.18, 1.81)* (p=0.31)	0.96 (0.35, 2.61) R ² =-37.57%, (p=0.91)	1.30 (0.34, 4.97) R ² =-21.93%, (p=0.61)	1.10 (0.06, 19.13)* (p=0.94)	0.94 (0.22, 4.11) R ² =-42.63%, (p=0.93)	0.50 (0.12, 2.04)* (p=0.30)	0.85 (0.14, 5.07) R ² =-28.48%, (p=0.82)	NR
Ticagrelor dose	1.28 (0.75, 2.20)* (p=0.33)	1.01 (0.26, 3.99) R ² =35.32%, (p=0.98)	0.32 (0.11, 0.87) R ² =75.25%, (p=0.03)	0.89 (0.13, 5.90)* (p=0.88)	1.22 (0.58, 2.55) R ² =-22.28%, (p=0.56)	0.98 (0.47, 2.05)* (p=0.94)	3.09 (1.32, 7.20) R ² =87.07%, (p=0.02)	1.54 (0.70, 3.36) R ² =100%, (p=0.18)
Language	2.48 (0.03, 246.59)* (p=0.67)	NR	NR	0.84 (0.03, 23.08)* (p=0.90)	6.73 (0.72, 63.22) R ² =17.11%, (p=0.07)	1.44 (0.28, 7.43)* (p=0.63)	NR	NR

*Adj R-squared = 0%

LVDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; NR, not reported; PAGr, platelet aggregation rate; PRU, platelet reaction units.

Heterogeneity analyses

Heterogeneity in the full meta-analysis without population stratification for the between study variance and the within study variance was shown. Therefore, meta-regression and subgroup analysis was required to explain the heterogeneity. From the results of the full meta-analysis, higher heterogeneity was found for LVEF, LVDD and PAGr, and the I² values were 72%, 84% and 87.7%, respectively. Therefore, we performed a meta-regression to explore the source of heterogeneity (tables 2 and 3, online supplementary figure S1). In accordance with data availability of the studies, factors analysed were: average age (≤60 years, >60 and ≤65 years, >65 years); region (China, Korea, Greece); follow-up (intervention effect ≤3 months, intervention effect ≥6 months); ticagrelor dose (45 mg twice daily, 60 mg twice daily, 90 mg once daily); and language (English, Chinese). We found that the dose of ticagrelor contributed a lot to the source of heterogeneity of LVDD and PAGr, and the corrected R² values were 75.25% and 87.07% (p=0.03 and p=0.02). No significant factors were observed for heterogeneity of LVEF in the meta-regression. There may be other potential factors causing heterogeneity. Heterogeneity in each subgroup was displayed by subgroup meta-analysis, and the results are shown in table 4 and online supplementary file 1. Age <65 years, Chinese studies and long term follow-up (≥6 months) were associated with greater efficacy and safety of low dose ticagrelor in ACS patients. A difference was found between the two doses of ticagrelor for PAGr (SMD -0.66, 95% CI -0.83 to -0.53; p<0.01), the I² statistic was reduced from 87.7% to 7.8%, without

altering the significance of the pooled effect size, when studies were restricted to those in which patients received ticagrelor 45 mg twice a day. A small sample size for each dose of ticagrelor in the studies may also be responsible for the heterogeneity of the results. This analysis included Chinese and English studies, and subgroup analysis showed that language differences did not affect the overall results. Gablbrait plot and Metaninf plot were also made to estimate the heterogeneity of the included studies and the impact of individual studies on the combined effect (see online supplementary figure S3 and figure S4).

Study quality and publication bias

The quality of the randomised studies, as assessed by the modified Jadad scale, ranged from moderate to high quality, with scores of 5–7 (see online supplementary table S1). A funnel plot of each trial's effect size was constructed by Begg's test and Egger's test to assess the possibility of publication bias (online supplementary figure S5, online supplementary table S2). No significant publication bias was found in the analysis (p>0.1). No study exceeding the 95% CI was shown in the funnel plot, and the studies gathered at the top of the funnel chart, which also suggests low selection bias or publication bias in this analysis.

DISCUSSION

This meta-analysis suggests that low dose ticagrelor could significantly reduce MACEs, increase LVEF and decrease LVDD

Table 3 Adjusted p value of multi-factor meta-regression analysis for the efficacy and safety of low dose ticagrelor in patients with acute coronary syndrome

Covariate	MACE	LVEF	LVDD	Major bleeding events	Minor or minimal bleeding events	Non-bleeding adverse events	PAGr	PRU
Average age	0.80	0.49	0.20	0.97	0.20	0.85	0.42	0.74
Region	1.00	NR	NR	1.00	0.83	0.22	NR	0.98
Follow-up	0.52	0.64	0.27	0.97	0.65	0.51	0.24	NR
Ticagrelor dose	0.75	1.00	0.04	1.00	0.78	0.98	0.02	0.24
Language	NR	NR	NR	1.00	0.99	0.17	NR	NR

Monte Carlo permutation test for meta-regression correction (permutations=10 000).

LVDD, Left ventricular end diastolic dimension; LVEF, Left ventricular ejection fraction; MACEs, Major adverse cardiac events; NR, Not reported; PAGr, platelet aggregation rate; PRU, Platelet reaction units.

Table 4 Subgroup analysis of efficacy and safety of low dose ticagrelor in patients with acute coronary syndrome according to patient characteristics

Subgroup	No of studies	N	MACE	LVEF	LVDD	Major bleeding events	Minor or minimal bleeding events	Non-bleeding adverse events	PAGr	PRU
Average age (years)										
≤60	4	286	0.33 (0.13, 0.83) I ² =0.0%, Z=2.36 (p=0.02)	0.87 (0.55, 1.22) I ² =81.7%, Z=5.19 (p<0.01)	-0.72 (-1.05, -0.40) I ² =0.0%, Z=4.34 (p<0.01)	1.00 (0.06, 15.99) I ² =0.0%, Z=0.00 (p=1.00)	9.35 (0.85, 102.30)* Z=1.83 (p=0.07)	0.36 (0.14, 0.97) I ² =17.2%, Z=2.01 (p=0.04)	-0.78 (-1.17, -0.40)* Z=3.98 (p<0.01)	-1.92 (-3.00, -0.84)* Z=3.49 (p<0.01)
>60 to ≤65	8	911	0.41 (0.25, 0.66) I ² =0.0%, Z=3.63 (p<0.01)	0.40 (0.23, 0.58) I ² =51.3%, Z=4.42 (p<0.01)	-0.25 (-0.42, -0.07) I ² =87.6%, Z=2.74 (p<0.01)	1.26 (0.43, 3.68) I ² =0.0%, Z=0.42 (p=0.67)	1.18 (0.65, 2.13) I ² =0.0%, Z=0.54 (p=0.59)	0.56 (0.33, 0.94) I ² =0.3%, Z=2.18 (p=0.03)	-1.04 (-1.73, -0.34) I ² =90.9%, Z=2.92 (p<0.01)	-2.48 (-2.95, -2.00) I ² =34.6%, Z=10.19 (p<0.01)
>65	4	389	0.40 (0.14, 1.14) I ² =2.2%, Z=1.72 (p=0.07)	NR	NR	0.29 (0.01 to 41.08)* Z=0.49 (p=0.62)	2.35 (1.11, 5.02) I ² =64.4%, Z=2.22 (p=0.03)	0.40 (0.18, 0.89) I ² =52.2%, Z=2.25 (p=0.02)	-0.35 (-0.63, -0.07)* Z=2.46 (p=0.01)	NR
Region										
China	13	1504	0.38 (0.26, 0.57) I ² =0.0%, Z=4.7 (p<0.01)	0.51 (0.35, 0.67) I ² =72.0%, Z=6.35 (p<0.01)	-0.36 (-0.52, -0.20) I ² =84.0%, Z=4.49 (p<0.01)	1.18 (0.40, 3.49) I ² =0.0%, Z=0.29 (p=0.77)	1.35 (0.83, 2.19) I ² =25.1%, Z=1.21 (p=0.23)	0.45 (0.30, 0.69) I ² =0.0%, Z=3.70 (p<0.01)	-0.86 (-1.30, -0.42) I ² =87.7%, Z=3.81 (p<0.01)	-2.80 (-3.68, -1.92)* Z=6.21 (p<0.01)
Korea	2	105	NR	NR	NR	1.10 (0.07, 17.60) I ² =0.0%, Z=0.07 (p=0.95)	8.89 (1.48, 53.28) I ² =0.0%, Z=2.39 (p=0.02)	2.23 (0.43, 11.54) I ² =0.0%, Z=0.96 (p=0.34)	NR	-2.64 (-2.93, -1.99) I ² =30.4%, Z=10.29 (p<0.01)
Greece	1	20	1.00 (0.02, 50.40)* Z=0.00 (p=1.00)	NR	NR	1.00 (0.02, 50.40)* Z=0.00 (p=1.00)	9.35 (0.85, 102.30)* Z=1.83 (p=0.07)	0.11 (0.01, 1.17)* Z=1.83 (p=0.07)	NR	-1.92 (-3.00, -0.84)* Z=3.49 (p<0.01)
Follow-up										
Intervention effect ≤3 months	9	665	0.62 (0.25, 1.55) I ² =0.0%, Z=1.02 (p=0.31)	0.47 (0.24, 0.70) I ² =88.0%, Z=4.03 (p<0.01)	-0.40 (-0.62, -0.17) I ² =75.2%, Z=3.46 (p<0.01)	0.85 (0.11, 6.67) I ² =0.0%, Z=0.16 (p=0.88)	1.64 (0.77, 3.50) I ² =36.4%, Z=1.27 (p=0.20)	0.70 (0.26, 1.91) I ² =31.4%, Z=0.70 (p=0.49)	-0.76 (-1.62, 0.09) I ² =90.1%, Z=1.76 (p=0.08)	-2.46 (-2.85, -2.07) I ² =9.2%, Z=12.46 (p<0.01)
Intervention effect ≥6 months	7	964	0.35 (0.22, 0.54) I ² =6.3%, Z=4.66 (p<0.01)	0.55 (0.33, 0.77) I ² =0.0%, Z=4.93 (p<0.01)	-0.32 (-0.54, -0.10) I ² =91.3%, Z=2.89 (p<0.01)	1.26 (0.42, 3.85) I ² =0.0%, Z=0.41 (p=0.68)	1.64 (0.92, 2.91) I ² =47.2%, Z=1.68 (p=0.09)	0.45 (0.29, 0.69) I ² =0.0%, Z=3.63 (p<0.01)	-0.92 (-1.55, -0.29) I ² =89.8%, Z=2.87 (p<0.01)	NR
Ticagrelor dose										
45 mg twice daily	7	240	0.32 (0.18, 0.58) I ² =0.0%, Z=3.78 (p<0.01)	0.58 (0.13, 1.03)* Z=2.54 (p=0.01)	0.61 (0.16, 1.06)* Z=2.67 (p=0.01)	1.19 (0.40, 3.51) I ² =0.0%, Z=0.31 (p=0.76)	1.08 (0.47, 2.45) I ² =0.0%, Z=0.17 (p=0.86)	0.42 (0.15, 1.18) I ² =36.8%, Z=1.64 (p=0.10)	-1.66 (-2.54, -0.77) I ² =83.7%, Z=3.67 (p<0.01)	-2.83 (-3.45, -2.21) I ² =0.0%, Z=8.94 (p<0.01)
60 mg twice daily	2	32	1.00 (0.02, 50.40)* Z=0.00 (p=1.00)	NR	NR	1.00 (0.02, 50.40)* Z=0.00 (p=1.00)	9.35 (0.85, 102.30)* Z=1.83 (p=0.07)	0.11 (0.01, 1.17)* Z=1.83 (p=0.07)	NR	-2.42 (-3.08, -1.76) I ² =24.7%, Z=7.16 (p<0.01)
90 mg once daily	8	484	0.45 (0.26, 0.78) I ² =0.0%, Z=2.84 (p<0.01)	0.50 (0.33, 0.67) I ² =77.5%, Z=5.83 (p<0.01)	-0.50 (-0.66, -0.33) I ² =62.9%, Z=5.79 (p<0.01)	1.05 (0.07, 16.78) I ² =0.0%, Z=0.03 (p=0.97)	1.81 (1.03, 3.19) I ² =58.5%, Z=2.05 (p=0.04)	0.52 (0.33, 0.80) I ² =0.0%, Z=2.95 (p<0.01)	-0.48 (-0.65, -0.30) I ² =7.8%, Z=5.37 (p<0.01)	-1.97 (-2.71, -1.23)* Z=5.19 (p<0.01)
Language										
English	4	165	1.00 (0.02, 50.40)* Z=0.00 (p=1.00)	NR	NR	1.06 (0.14, 10.25) I ² =0.0%, Z=0.05 (p=0.96)	9.05 (2.16, 37.97) I ² =0.0%, Z=3.01 (p<0.01)	0.52 (0.16, 1.66) I ² =51.6%, Z=1.11 (p=0.27)	NR	-2.46 (-2.85, -2.07) I ² =9.2%, Z=12.46 (p<0.01)
Chinese	12	1464	0.38 (0.26, 0.57) I ² =0.0%, Z=4.66 (p<0.01)	0.51 (0.35, 0.67) I ² =72.0%, Z=6.35 (p<0.01)	-0.36 (-0.52, -0.20) I ² =84.0%, Z=4.49 (p<0.01)	1.18 (0.40, 3.49) I ² =0.0%, Z=0.29 (p=0.77)	1.35 (0.83, 2.19) I ² =25.1%, Z=1.20 (p=0.23)	0.47 (0.31, 0.73) I ² =0.0%, Z=3.44 (p<0.01)	-0.86 (-1.30, -0.42) I ² =87.7%, Z=3.81 (p<0.01)	NR

* Data was available in only one study.

LVDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; NR, not reported; PAGr, platelet aggregation rate; PRU, P2Y12 reaction units.

compared with standard dose clopidogrel in ACS patients. No differences for the risk of major bleeding events were shown between the two groups. Less incidence of minor or minimal bleeding events and AEs was observed in the low dose ticagrelor group. In addition, low dose ticagrelor was associated with lower platelet aggregation compared with standard dose clopidogrel.

The platelet inhibition and patient outcomes (PLATO) study, an important clinical study involving 18 624 patients from different countries and centres, showed that ticagrelor significantly reduced cardiovascular death, myocardial infarction and stroke events compared with clopidogrel (absolute risk reduction 16%, relative risk reduction 16%, $p < 0.001$, numbers needed to treat=54). Also, the risk of MACEs with ticagrelor decreased in the early stage and was maintained throughout the 1 year treatment.^{4 27–29} Ticagrelor did not increase major bleeding or fatal/life threatening major bleeding. Ticagrelor related dyspnoea events were higher than those with clopidogrel, but most events were mild to moderate and could be relieved without treatment. However, ticagrelor increased the risk of minor or minimal bleeding events compared with clopidogrel, resulting in a reduction in patient compliance, which could increase the incidence of MACEs.

The PLATO study showed that ticagrelor has great efficacy and safety in ACS patients compared with clopidogrel. However, the PLATO study mainly comprised Western patients, which has limitations. A large number of clinical studies have demonstrated that the clinical efficacy of ticagrelor in East Asian ACS patients is significantly different from that in Western patients.^{30 31} The PHILO (phase the international study of ticagrelor and clinical outcomes in Asian ACS patients) study compared the efficacy and safety of ticagrelor and clopidogrel in ACS patients in East Asia, which was designed in the same way as the PLATO study. In the PHILO study, ticagrelor increased composite events for cardiovascular death, myocardial infarction and stroke compared with clopidogrel (9.0% vs 6.3%, HR=1.47, 95% CI 0.88 to 2.44). Also, the incidence of bleeding events caused by ticagrelor was higher than that for clopidogrel (10.3% vs 6.8%, HR=1.54, 95% CI 0.94 to 2.53), which may be related to the low body mass index in East Asian. AEs were more common in the ticagrelor group.^{32 33}

The PHILO study showed that ticagrelor does not have an advantage over clopidogrel in ACS patients from East Asia.³⁴ Can low doses of ticagrelor reduce adverse events? Our meta-analysis assessed the efficacy and safety of low dose ticagrelor compared with standard dose clopidogrel in ACS patients. In the current analysis, low dose ticagrelor also reduced the incidence of MACEs, did not increase major bleeding events and reduced the incidence of minor or minimal bleeding events and AEs compared with standard dose clopidogrel.

According to the results of this meta-analysis, the different mechanisms of action of ticagrelor and clopidogrel may lead to different outcomes. Clopidogrel, a thienopyridine prodrug, selectively inhibits the binding of ADP to its platelet receptor and secondary ADP mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.^{1 35} Ticagrelor, an oral P2Y₁₂ inhibitor, can bind reversibly to its platelet receptor with a more rapid onset of action and a faster recovery of platelet function. It is preferable to use ticagrelor rather than clopidogrel in ACS patients undergoing an early invasive or ischaemia guided strategy.^{32–34 36}

The guidelines recommended that in all ACS patients without contraindications, the ticagrelor protocol should be carried out (180 mg loading dose, then 90 mg twice daily) for up to 12 months.^{1 29 35} If it is not appropriate for some patients to take ticagrelor because of hypersensitivity or major bleeding events, a loading dose of clopidogrel should be taken, and then a daily

maintenance dose (300 mg or 600 mg loading dose, and then 75 mg daily).^{6 17}

A recently published review put forward the concept of 'East Asian paradox'.³⁷ Compared with Westerners, East Asians have a higher incidence of warfarin related intracranial haemorrhage. Therefore, different a target for the international normalised ratio (INR) has been proposed and has been adjusted in clinical

Main messages

- ▶ Acute coronary syndrome (ACS) is a common cardiovascular disease that has a high incidence and mortality rate, which seriously affects the quality of life and life expectancy of patients.
- ▶ Dual antiplatelet therapy as an effective treatment for ACS patients can reduce platelet reactivity and prevent ischaemic events, and forms the cornerstone of treatment for patients with ACS.
- ▶ It is recognised that ticagrelor significantly reduced cardiovascular death, myocardial infarction and stroke events compared with clopidogrel. Ticagrelor did not increase major bleeding or fatal/life threatening major bleeding. However, the incidence of bleeding events was higher in the ticagrelor group than in the clopidogrel group in East Asian ACS patients, which may be related to issues such as low body mass index and ethnic differences in thrombogenicity in East Asians.

Current research questions

- ▶ Efficacy and safety of aspirin plus ticagrelor 60 mg long term dual antiplatelet therapy in coronary heart disease patients with high risk factors for ischaemia.
- ▶ The significance of cardiac MRI in evaluating viable myocardium in patients with coronary heart disease.
- ▶ The risk of bleeding events of rivaroxaban on the basis of antiplatelet therapy in patients with atrial fibrillation after percutaneous coronary intervention.

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Self assessment questions

1. Dual antiplatelet therapy (DAPT) is the cornerstone of treatment for patients with acute coronary syndrome (ACS).
2. The present guidelines recommend that DAPT should last for 2 years.
3. Compared with clopidogrel, ticagrelor has better effectiveness and reduces the incidence of cardiovascular event recurrence in ACS patients with percutaneous coronary intervention.
4. Ticagrelor is an oral P2Y₁₂ inhibitor bound reversibly to its platelet receptor, has a more rapid onset of action and a faster recovery of platelet function.
5. The plausible explanations for the higher incidence of bleeding events in the ticagrelor group compared with the clopidogrel group in East Asian ACS patients which may be related to low body mass index, ethnic differences in thrombogenicity in East Asian and gene–environment interactions.

practice in East Asia (1.6–2.6). Similarly, a large number of clinical data have indicated that the incidence of ischaemic events in East Asians may be similar or even lower compared with Westerners. In contrast, East Asians seem to have a higher risk of bleeding than Westerners.^{38 39}

Differences in the effects of coagulation, fibrinolysis and inflammation markers on thrombogenicity among races may be one of the causes of the East Asian paradox.^{37 40 41} One potential mechanism is the difference in genetic polymorphisms among different races. In order to evaluate important variables of the clopidogrel response, we reviewed numerous pharmacodynamic studies and clinical evidence, which found that the cytochrome P450 (CYP) 2C19 loss of function allele was the main indicator of platelet reactivity during treatment with clopidogrel.^{42–44} These hypercoagulable factors also exhibit different clinical characteristics, which are regulated by gene–environment interactions.^{38 39}

Li *et al* conducted a study of 90 mg and 180 mg doses of ticagrelor in healthy people in China. The study showed that the maximum plasma concentration and maximum area of the plasma concentration–time curve for ticagrelor (90 mg twice per day) and its active metabolite (AR-C124910XX) in healthy Chinese volunteers were usually 40% higher than that in Caucasians.^{10 45} Recent studies showed that low dose ticagrelor may have sufficient inhibitory effect on platelet aggregation in Chinese patients with ACS. Our meta-analysis obtained similar results. Avoiding a loading dose of ticagrelor might prevent bleeding events, which may have important clinical significance in the treatment and management of ACS patients in East Asia.

Our meta-analysis mainly involved East Asian patients. The results showed that low dose ticagrelor decreased MACEs and did not increase the risk of major bleeding in ACS patients compared with standard dose clopidogrel, and the rates of minor or minimal bleeding events and AEs events also decreased. This can greatly improve compliance in patients with ACS in East Asia, which will decrease the incidence of MACEs. Low dose ticagrelor may be more suitable for East Asians.

A few potential limitations may exist in this meta-analysis. Some important confounding factors might affect the final results, such as study design, follow-up time, inclusion and exclusion criteria, and ticagrelor dose. For example, the various definitions of MACEs may obscure possible differences in their components. Most of the included studies were positive, which might result in publication bias. In view of the issues mentioned, the authors' conclusions should be treated with caution.

CONCLUSIONS

On the basis of this meta-analysis, it could be concluded that low dose ticagrelor has a considerable safety and efficacy profile and decreased MACEs and did not increase the risk of major bleeding in ACS patients compared with standard dose clopidogrel. In addition, low dose ticagrelor had lower platelet aggregation compared with standard dose clopidogrel. Therefore, for clinical efficacy and safety, it is necessary to perform large scale clinical trials to identify the optimal antiplatelet regimen and therapeutic level of platelet reactivity.

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Contributors TX was responsible for the plan for the current study. TX and QC formulated specific search strategy and looked through Pubmed, Embase, the Cochrane Library and other databases in detail for relevant publications. Three independent researchers (ZW, SW and HZ) reviewed the study titles and abstracts, and potentially relevant articles satisfying the inclusion criteria were reviewed in detail. Trials selected for data extraction and detailed analysis were analysed by two researchers (QC and YW). Disagreements were resolved by a third researcher (CL). QC, YZ and CL performed the meta-analysis for the included studies through Stata (V.11.0). HX and CW assisted in interpreting the results. QC and YZ drafted the manuscript. TX and DL evaluated the data quality and approved the final version of the manuscript for submission. All authors have critically reviewed the manuscript.

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Answers

1. True
2. False
3. True
4. True
5. True