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Efficacy and Safety of Ticagrelor in East Asian Patients with Acute Coronary Syndrome: A Meta-Analysis of Randomized Controlled Trials

META-ANALYSIS

ABSTRACT

Background: Although current guidelines recommend ticagrelor to clopidogrel for patients with acute coronary syndrome, its benefit and risk are unclear for East Asians. This meta-analysis was performed to assess the efficacy and safety of ticagrelor in East Asian patients with acute coronary syndrome.

Methods: Medline, EMBASE, and Cochrane Databases were searched from inception to July, 2021, for randomized controlled trials comparing ticagrelor with clopidogrel in East Asian patients with acute coronary syndrome. Major adverse cardiovascular events and bleeding events were assessed by using Mantel-Haenszel-pooled risk ratio and 95% confidence interval.

Results: Five randomized controlled trials identified 2752 patients with acute coronary syndrome. Compared with clopidogrel, ticagrelor had no statistical difference of major adverse cardiovascular events (RR 0.87; 95% CI 0.52-1.45; $P = .58$), all cause death (RR 0.90, 95% CI 0.62-1.32; $P = .60$), cardiovascular death (RR 0.90, 95% CI 0.47-1.72; $P = .74$), myocardial infarction (RR 0.91, 95% CI 0.52-1.58; $P = .73$), and stroke (RR 0.87, 95% CI 0.48-1.57; $P = .64$). Despite ticagrelor did not increase the incidence of fatal bleeding (RR 2.49, 95% CI 0.79-7.87; $P = 0.12$), the risks of all bleeding (RR 1.71, 95% CI 1.36-2.16; $P < .00001$), major bleeding (RR 1.51, 95% CI 1.12-2.04; $P = .007$), non-coronary artery bypass grafting major bleeding (RR 1.83, 95% CI 1.23-2.71; $P = .003$), and minor bleeding (RR 1.92, 95% CI 1.40-2.64; $P < .0001$) were significantly higher.

Conclusions: Although there was no significant difference in the incidence of fatal bleeding, ticagrelor displayed similar efficacy and dramatically increased the risk of other bleeding events.

Keywords: Ticagrelor, East Asian, acute coronary syndrome, randomized controlled trial, meta-analysis

INTRODUCTION

A combination of aspirin and a kind of $P2Y_{12}$ inhibitor as dual antiplatelet therapy (DAPT) is the cornerstone of secondary prevention in patients with acute coronary syndrome (ACS). Ticagrelor is a reversible non-thienopyridine oral $P2Y_{12}$ inhibitor that provides faster, more potent, and consistent platelet inhibition than clopidogrel.[1] Based on the Platelet Inhibition and Patient Outcomes (PLATO) trial,[2] the European Society of Cardiology (ESC) guidelines[3,4] consider to use clopidogrel only when ticagrelor is not available, cannot be tolerated, or is contraindicated (I, C). Similarly, the American College of Cardiology (ACC)/American Heart Association (AHA) guideline[5] recommends to use ticagrelor in preference to clopidogrel for maintenance of $P2Y_{12}$ inhibitor therapy (IIa, B).

East Asians are the most populous race in the world with over 1.6 billion people. In the contemporary trials of antithrombotic treatment, East Asian patients with ACS show a similar or even lower rate of ischemic event and higher bleeding risk compared with Caucasian patients, which is referred to as the "East Asian Paradox."[6,7] Besides, different net clinical benefits have been observed between the races with $P2Y_{12}$ inhibitors that may be related to racial differences in

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pharmacokinetic and pharmacodynamic profiles.[8,9] Even so, the current DAPT recommendation in East Asia[10-13] are mainly based on the American or European guidelines. In order to provide evidence for "race-tailored" DAPT in East Asian patients with ACS, we conducted a meta-analysis to assess the efficacy and safety of ticagrelor in the specific race.

METHODS

Literature Search

We systematically searched Medline, EMBASE, and Cochrane Databases for all relevant articles comparing ticagrelor with clopidogrel in East Asian patients with ACS through July, 2021. Literature was searched with the following keywords: ticagrelor, clopidogrel, coronary disease, coronary artery disease, coronary heart disease, acute coronary syndrome, myocardial infarction, unstable angina, and random*. A comprehensive search of reference lists of all review articles and original studies retrieved by this method was performed to identify additional studies.

Selection Criteria

The inclusion criteria were the following: (1) trials designed as RCT; (2) trials based on East Asian patients with ACS; (3) trials compared ticagrelor with clopidogrel; (4) trials reported 6-month or longer outcomes; and (5) outcomes included ischemic events and/or bleeding events.

Data Abstraction

Two investigators independently assessed studies for possible inclusion by reading titles and/or abstracts, then viewed the full-texts of the remaining publications to pick up the ultimately available studies. Data extraction was done by 1 reviewer, and subsequently cross-checked by the other reviewer. Any divergences were discussed or determined by a third investigator. The following informations were abstracted: the first author and publication year, country, sample size, baseline features of patients, treatment features, follow-up time, efficacy outcomes, and/or safety outcomes and their definitions.

Bias Risk and Study Quality Assessment

The methodological quality of eligible studies was assessed by the Cochrane collaboration's tool for assessing risk of bias including the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. The bias risk of each study was scored as low, unclear, or high in each section.

Statistical Analysis

Dichotomous data were expressed risk ratio (RR) with 95% CI. Heterogeneity of effect size across the studies was tested using Q statistics at the $P < .10$ level of significance. We also calculated the I^2 statistic with a quantitative measure of inconsistency across the studies. The data were pooled by random-effects model in case of significant heterogeneity (Cochran test with $P < .10$ or $I^2 > 50\%$) was found. Otherwise, the fixed-effects model was used. Sensitivity analyses with fixed-effect models were performed to assess consistency among effect estimates that were obtained with random- and fixed-effects models. Potential publication bias was visually inspected by funnel plot if more than 10 studies. We conducted subgroup analyses according to sex (male and female), age (<65 years and ≥65 years), weight (<60 kg and ≥60 kg), body mass index (BMI) (<25 kg/m^2 and ≥25 kg/m^2), and clinical presentation [ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction–ACS (NSTEMI–ACS)]. Meta-analysis was performed with the software of Cochrane Review Manager 5.1.2 (Cochrane Library Software, Oxford, UK).

RESULTS

Literature Retrieval, Information Extraction, and Bias Risk Assessment

Figure 1 shows a flow diagram for the selection process. A total of 5 RCTs[14-18] that included 2752 patients (ticagrelor = 1379 vs. clopidogrel = 1373) were finally identified. Table 1 summarizes the characteristics of the selected studies. Among the 5 RCTs, two studies were based on patients from China,[16,17] one study was based on patients from Korea,[18] and the other two studies were based on patients from different East Asian countries.[14,15] Four studies were multicenter trial[14,15,17,18] and one was single center trial that only including patients older than 65 years.[16] Four studies included three types of ACS patients using PLATO bleeding criteria and were followed up for 12 months,[14-16,18] while one study included only STEMI patients using Thrombolysis in myocardial infarction (TIMI) bleeding criteria and was followed up for 6 months.[17] The methodological quality of the included studies was good in general as shown in Table 1.

Efficacy and Safety Analyses

Our pooled analysis indicated that ticagrelor did not reduce the incidence of MACE (RR 0.87, 95% CI 0.52-1.45; $P = .58$), all cause death (RR 0.90, 95%CI 0.62-1.32; $P = .60$), cardiovascular death (RR 0.90, 95% CI 0.47-1.72; $P = 0.74$), myocardial infarction (RR 0.91, 95% CI 0.52-1.58; $P = .73$), and stroke (RR 0.87, 95% CI 0.48-1.57; $P = .64$) (Figure 2). In terms of the safety outcomes, although ticagrelor did not increase the incidence of fatal bleeding (RR 2.49, 95% CI 0.79-7.87; $P = .12$), it significantly increased the risk of all bleeding (RR 1.71, 95% CI 1.36-2.16; $P < .00001$), major bleeding (RR 1.51, 95% CI 1.12-2.04; $P = .007$), non-CABG major bleeding (RR 1.83, 95% CI 1.23-2.71; $P = .003$), and minor bleeding (RR 1.92, 95%CI 1.40-2.64; $P < .0001$) (Figure 3).

HIGHLIGHT

- Five studies with 2752 East Asian patients with acute coronary syndrome were included.
- We compared the efficacy and safety between ticagrelor and clopidogrel.
- We did subgroup analyses according to patients' baseline clinical presentations.
- Ticagrelor increased the risk of bleeding without reduced ischemic events.

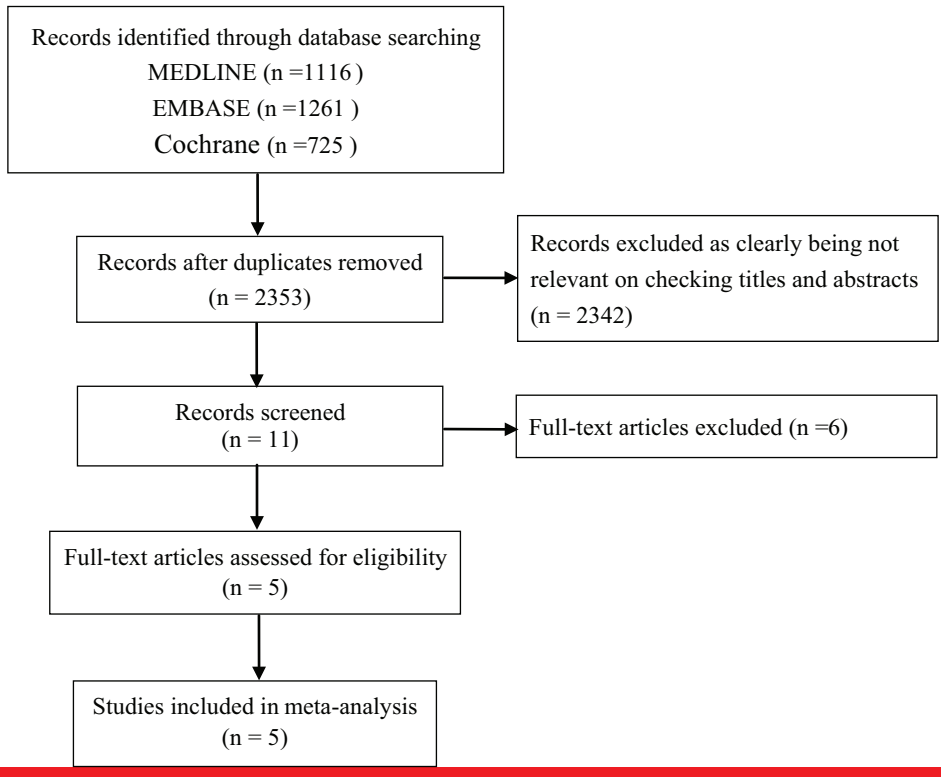


Figure 1. Study selection according to the PRISMA model.

Subgroup Analyses

To explore the study heterogeneity, we further performed meta-analysis in subgroups based on several baseline clinical presentations (sex, age, weight, BMI, and clinical presentation). Table 2 shows a similar risk of MACE in females (RR 1.17, 95% CI 0.68-4.62; $P = .64$), in patients <65 years and ≥ 65 years (RR 0.64, 95% CI 0.27-1.54; $P = .32$ and RR 1.14, 95% CI 0.23-5.77; $P = .87$, respectively), in patients with BMI <25 kg/m^2 and ≥25 kg/m^2 (RR 1.56, 95% CI 0.99-2.44; $P = .05$ and RR 1.39, 95% CI 0.79-2.46; $P = .26$, respectively), and in patients with STEMI and NSTEMI-ACS (RR 0.94, 95% CI 0.37-2.40; $P = .90$ and RR 1.51, 95% CI 0.91-2.48; $P = .11$, respectively). Only in males' subgroup, ticagrelor did significantly reduce the risk of MACE (RR 1.65, 95% CI 1.09-2.51; $P = .02$) (Table 2).

Sensitivity Analyses

There was no difference in the results between the fixed-effect model and the random-effect model for the efficacy and safety outcomes.

DISCUSSION

The major pathophysiological mechanism underlying ACS is atherosclerotic plaque rupture with resultant coronary thrombosis, and therefore, antiplatelet therapy is an important foundation in the treatment and prevention of recurrence of ACS.[19] The optimal antiplatelet therapy aims to prevent thrombosis while avoiding hemorrhage. Since clopidogrel has substantial limitations in the management of ACS with a modest inhibition of platelet aggregation and a delayed onset and offset of action,[20,21] ticagrelor is now preferred to clopidogrel as a first-line therapy in DAPT, as endorsed by both European and US guidelines.

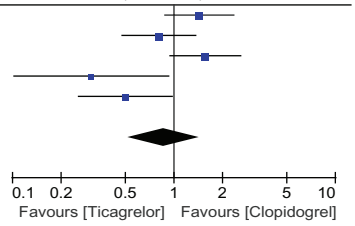
However, a recent retrospective observational analysis of net adverse clinical events (NACE) in patients with ACS-indicated ticagrelor was not associated with significant difference in the risk of NACE but dramatically increased the risk of hemorrhagic events.[22] Meanwhile, a recent network meta-analysis compared clopidogrel, ticagrelor, and prasugrel in patients with ACS-indicated ticagrelor significantly reduced the risk of ischemic events at the cost of increased major bleeding, but its direct pairwise meta-analysis showed there was no statistically significant differences in major bleeding risk between ticagrelor and clopidogrel.[23] Thus, whether ticagrelor would increase the risk of major bleeding remains to be further discussed. In addition, there are significant differences between East Asian and Western patients in terms of physique, thrombogenicity, hemorrhagic diathesis, and on-treatment platelet reactivity.[24] Although earlier meta-analysis had assessed ticagrelor and clopidogrel in East Asian patients with ACS, it included only 3 RCTs and fewer outcomes were synthesized.[25] Therefore, whether the evidence and guidelines from Western countries can be generalized to East Asian patients remains largely unclear.

In this meta-analysis, we assessed the efficacy and safety of ticagrelor in East Asian patients with ACS, investigating the differences in treatment effects according to different baseline clinical presentations. The main findings of this meta-analysis were as follows: (1) ticagrelor displayed similar efficacies in MACE and its individual components; (2) although ticagrelor did not increase the incidence of fatal bleeding, the risks of other bleeding events were significantly higher; and (3) in males the benefit of ticagrelor appears to be

A. Composite of cardiovascular death, myocardial infarction or stroke

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
Goto S, et al 2015	36	401	25	400	23.0%	1.44 [0.88, 2.35]
Kang HJ, et al 2015	23	278	28	273	22.3%	0.81 [0.48, 1.36]
Park DW, et al 2019	36	400	23	400	22.7%	1.57 [0.95, 2.59]
Tang X, et al 2016	4	200	13	200	12.5%	0.31 [0.10, 0.93]
Wang H, et al 2016	11	100	22	100	19.5%	0.50 [0.26, 0.98]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.87 [0.52, 1.45]**
Total events	110		111			

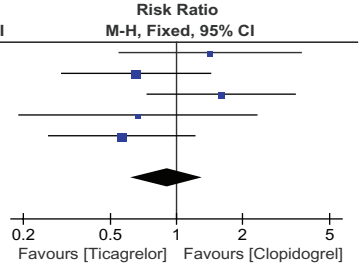
Heterogeneity: Tau² = 0.24; Chi² = 14.28, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 0.55 (P = 0.58)



B. All cause death

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goto S, et al 2015	10	401	7	400	12.9%	1.43 [0.55, 3.71]
Kang HJ, et al 2015	10	278	15	273	28.0%	0.65 [0.30, 1.43]
Park DW, et al 2019	16	400	10	400	18.5%	1.60 [0.74, 3.48]
Tang X, et al 2016	4	200	6	200	11.1%	0.67 [0.19, 2.33]
Wang H, et al 2016	9	100	16	100	29.6%	0.56 [0.26, 1.21]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.90 [0.62, 1.32]**
Total events	49		54			

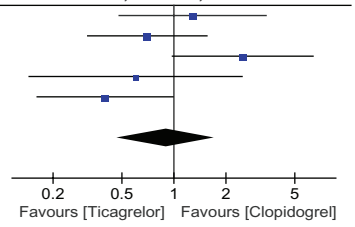
Heterogeneity: Chi² = 5.29, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 0.53 (P = 0.60)



C. Cardiovascular death

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
Goto S, et al 2015	9	401	7	400	20.2%	1.28 [0.48, 3.41]
Kang HJ, et al 2015	10	278	14	273	23.9%	0.70 [0.32, 1.55]
Park DW, et al 2019	15	400	6	400	21.0%	2.50 [0.98, 6.38]
Tang X, et al 2016	3	200	5	200	13.4%	0.60 [0.15, 2.48]
Wang H, et al 2016	6	100	15	100	21.6%	0.40 [0.16, 0.99]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.90 [0.47, 1.72]**
Total events	43		47			

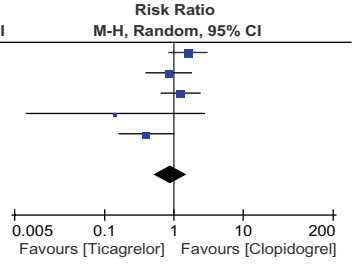
Heterogeneity: Tau² = 0.30; Chi² = 8.86, df = 4 (P = 0.06); I² = 55%
Test for overall effect: Z = 0.33 (P = 0.74)



D. Myocardial infarction

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
Goto S, et al 2015	24	401	15	400	27.0%	1.60 [0.85, 3.00]
Kang HJ, et al 2015	12	278	14	273	23.5%	0.84 [0.40, 1.79]
Park DW, et al 2019	20	400	16	400	26.6%	1.25 [0.66, 2.38]
Tang X, et al 2016	0	200	3	200	3.2%	0.14 [0.01, 2.75]
Wang H, et al 2016	6	100	15	100	19.7%	0.40 [0.16, 0.99]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.91 [0.52, 1.58]**
Total events	62		63			

Heterogeneity: Tau² = 0.19; Chi² = 8.40, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 0.35 (P = 0.73)



E. Stroke

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goto S, et al 2015	9	401	6	400	26.1%	1.50 [0.54, 4.16]
Kang HJ, et al 2015	2	278	4	273	17.5%	0.49 [0.09, 2.66]
Park DW, et al 2019	6	400	5	400	21.7%	1.20 [0.37, 3.90]
Tang X, et al 2016	1	200	5	200	21.7%	0.20 [0.02, 1.70]
Wang H, et al 2016	2	100	3	100	13.0%	0.67 [0.11, 3.90]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.87 [0.48, 1.57]**
Total events	20		23			

Heterogeneity: Chi² = 3.71, df = 4 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

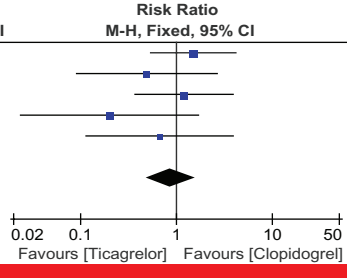
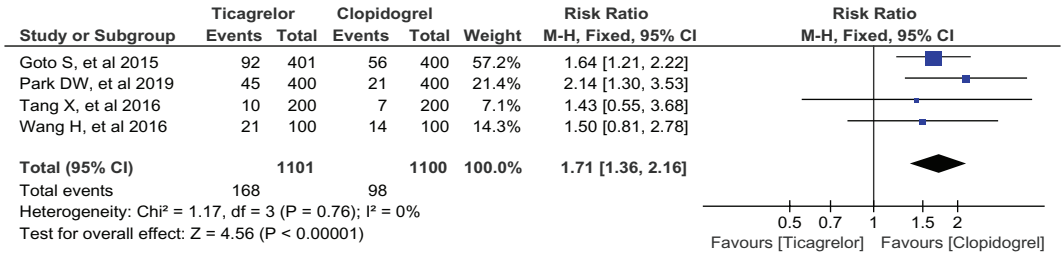
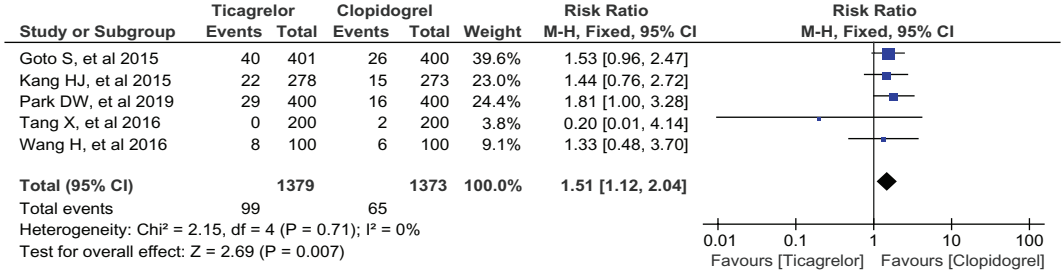


Figure 2. Forest plot of efficacy outcomes.

A. All bleeding

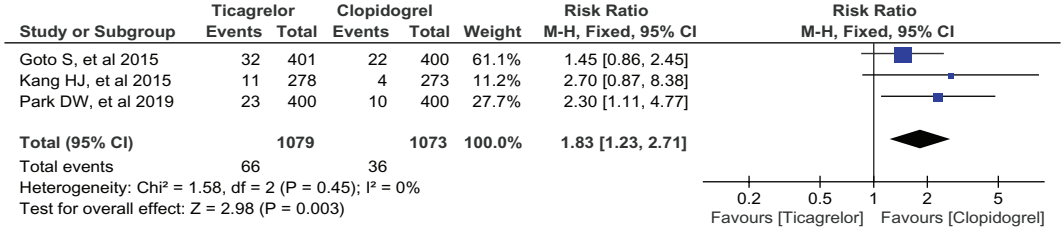


B. Major bleeding



C. Fatal bleeding

D. Non-CABG major bleeding



E. Minor bleeding

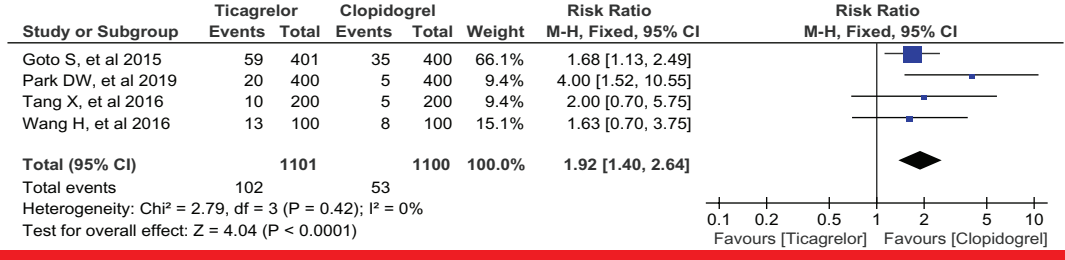


Figure 3. Forest plot of safety outcomes.

Table 1. Characteristics of the Included Studies

Authors	Publication Year	Country (%)	Sample Size (I/C)	Follow-Up (months)	Age (I/C, Years)	Male (I/C, %)	BMI (I/C, kg/m^2)	STEMI (I/C, %)	NSTEMI (I/C, %)	UA (I/C, %)	Smoker (I/C, %)	Hypertension (I/C, %)	Dyslipidemia (I/C, %)
Kang et al[14]	2015	Korea (NA)/ China (NA)	278/273	12	60/61*	75/72*	24/24*	46/45*	38/35*	13/16*	41/38*	60/62*	31/35*
Goto et al[15]	2015	Japan (90)/ China (4)/ Korea (6)	401/400	12	67/66	76/77	24/24	51/53	17/19	30/27	38/39	76/73	78/72
Wang et al[16]	2016	China (100)	100/100	12	79/80	69/66	NA	37/32	44/47	19/21	37/41	79/82	84/79
Tang et al[17]	2016	China (100)	200/200	6	64/64	71/73	NA	100/100	0/0	0/0	58/62	61/58	44/37
Park et al[18]	2019	Korea (100)	400/400	12	63/62	74/76	25/25	43/39	37/39	21/22	37/35	56/48#	52/49

Table 1. Characteristics of the Included Studies (continued)

Authors	Diabetes (I/C, %)	History of stroke (I/C, %)	Prior MI (I/C, %	Prior PCI (I/C, %)	Prior CABG (I/C, %)	Treated with PCI (I/C, %)	β-Blocker (I/C, %)	CCB (I/C, %)	ACEI/ARB (I/C, %)	Statin (I/C, %)	Nitrates (I/C, %)	PPI (I/C, %)	Bleeding Criteria	Study Quality
Kang et al[14]	29/30*	7/6*	12/18*	8/8*	1/2*	NA	52/57*	15/17*	62/65*	76/74*	NA	36/34*	PLATO	Low risk
Goto et al[15]	38/31	7/7	8/8	11/11	1/0	85/85	10/11	29/27	42/40	54/51	88/86	42/44	PLATO	Low risk
Wang et al[16]	42/39	11/10	17/15	3/6	0/0	75/71	69/74	69/63	61/67	83/79	90/89	31/33	PLATO	Low risk
Tang et al[17]	29/21	16/17	8/5	NA	NA	100/100	41/48	NA	38/47	99/100	86/88	NA	TIMI	Low risk
Park et al[18]	29/25	6/4	6/5	8/10	1/1	82/86	69/74	23/23	41/43	89/92	NA	3/2	PLATO	Low risk

I, intervention group; C, control group; BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PPI, proton pump inhibitor; PLATO, platelet inhibition and patient outcomes trial; TIMI, thrombolysis in myocardial infarction; NA, not available; *data of all Asian population including East Asians and Southeast Asians; #$P < .05$.

Table 2. Subgroup Analyses for Composite of Cardiovascular Death, Myocardial Infarction or Stroke (RR, 95% CI; P)

Subgroup		Composite of Cardiovascular Death, Myocardial Infarction, or Stroke
Sex	Male	1.65 (1.09-2.51); 0.02
	Female	1.17 (0.68-4.62); 0.64
Age	<65 years	0.64 (0.27-1.54); 0.32
	≥65 years	1.14 (0.23-5.77); 0.87
Weight	<60 kg	1.70 (0.94-3.06); 0.08
	≥60 kg	1.41 (0.91-2.19); 0.12
Body mass index	<25 kg/m^2	1.56 (0.99-2.44); 0.05
	≥25 kg/m^2	1.39 (0.79-2.46); 0.26
Clinical presentation	STEMI	0.94 (0.37-2.40); 0.90
	NSTEMI-ACS	1.51 (0.91-2.48); 0.11

STEMI, ST-segment elevation myocardial infarction; NSTEMI-ACS, non-ST-segment elevation myocardial infarction-acute coronary syndrome.

favorable, while the risk of bleeding cannot be assessed due to lack of data. Earlier studies found a higher rate of MACE in females,[26,27] which might be related to females more often present with atypical symptoms and signs.[28] Recent study demonstrated that females after myocardial infarction had higher rates of cardiovascular mortality and all-cause mortality than male, even after adjustment for potential confounders, including baseline health status.[29] (4) A similar risk of MACE was observed in females, in patients <65 years and ≥65 years, in patients with BMI < 25 kg/m^2 and ≥25 kg/m^2, and in patients with STEMI and NSTEMI-ACS.

Our findings were consistent with recent observational studies performed in East Asian. The Comparison of Efficacy and Safety Between TIcagrelor and Clopidogrel In Chinese (COSTIC) study showed the patients prescribed with ticagrelor had a similar incidence of MACE and a higher incidence of bleeding relative to those with clopidogrel at 6 months and 12 months.[30] Another Korean nationwide cohort study of 70,715 patients with ACS demonstrated that, compared with clopidogrel, the use of ticagrelor was significantly associated with a higher incidence of bleeding at 2 years but no significant difference in composite ischemic events.[31]

We acknowledge that our meta-analysis had several limitations. First, despite we had systematically searched and reviewed relevant articles, the sample size was relatively small. Second, because of limited data, subgroup analysis of patients from different countries was not performed. Third, given the limited number of studies included in the analysis, our findings should be confirmed with future research.

CONCLUSIONS

Although there was no significant difference in the incidence of fatal bleeding, ticagrelor displayed similar efficacy and dramatically increased the risk of other bleeding events.

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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