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Efficacy and Safety of Novel Oral $P2Y_{12}$ Receptor Inhibitors in Patients With ST-Segment Elevation Myocardial Infarction Undergoing PCI: A Systematic Review and Meta-Analysis

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Abstract: The efficacy and safety of novel oral $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) are subjects of contention in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI, and the optimal duration of therapy remains uncertain. We searched PubMed, Embase, Cochrane Library, CNKI, VIP, and WanFang Data to identify randomized controlled trials comparing novel oral $P2Y_{12}$ receptor inhibitors with clopidogrel in patients with STEMI undergoing PCI until February 2016. The primary efficacy and safety endpoint were all-cause mortality and major/minor bleeding. Twelve studies were included. Novel oral $P2Y_{12}$ inhibitors significantly reduced the incidence of all-cause death (relative risk: 0.65, 95% confidence interval, 0.53–0.78), major adverse cardiac events [0.68 (0.56–0.83)], and stent thrombosis [0.56 (0.43–0.75)] without significant difference in bleeding ($P = 0.11$) compared with clopidogrel. Identical results were observed in the longer dual antiplatelet therapy (DAPT) and shorter-DAPT subgroups, albeit Chinese patients with ticagrelor treatment had a slight increase in bleeding ($P = 0.08$). Furthermore, the pooled relative risk ratio for each endpoint showed no significant difference between the longer-DAPT and shorter-DAPT subgroups. In conclusion, prasugrel and ticagrelor decreased the risk of all-cause death, major adverse cardiac events, and stent thrombosis without causing more bleeding events compared with clopidogrel in patients with STEMI undergoing PCI.

Key Words: prasugrel, ticagrelor, ST, percutaneous coronary intervention, meta-analysis, therapy

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INTRODUCTION

Coronary atherosclerosis is a prerequisite for acute coronary syndrome (ACS), after plaque rupture/erosion, platelets undergo a remarkably complex series of biological procedure to form stable platelet aggregates, which eventually produces a thrombus occluding coronary blood flow caused a stable and occlusive thrombus typically results in ST-elevation myocardial infarction (STEMI).[1,2] Before PCI and after surgery, it is necessary to inhibit platelet aggregation by using antiplatelet therapy to prevent stent thrombosis during vascular healing and endothelial repair.[3] Dual antiplatelet therapy (DAPT), which involves a combination of aspirin and a $P2Y_{12}$ inhibitor, is widely recommended for preventing thrombotic complications after percutaneous coronary intervention (PCI) in patients with STEMI.[4] Currently, the most widely used agent is clopidogrel, which has certain limitations such as requirement of transformation in the liver, irreversible platelet inhibition resulting in a delayed onset of antiplatelet effect, and variabilities in antiplatelet response.[5] Therefore, physicians need to know the pharmacokinetic characteristics of antiplatelet drugs to compensate for the above shortcomings.

In the PLATO trial, ticagrelor was observed to cause a significant reduction in death, myocardial infarction (MI), and stent thrombosis without increasing major bleeding, although it resulted in a higher rate of stroke.[6] These were attributed to its faster, greater, and more consistent action than that of clopidogrel.[7] Similarly, prasugrel, a third-generation thienopyridine, which is more efficiently metabolized and provides a more potent platelet inhibition with less intersubject variability,[8] has been proven by clinical trials as more effective than clopidogrel in preventing ischemic events without an apparent increase in bleeding among patients with STEMI undergoing PCI.[9] However, one trial demonstrated that although prasugrel was associated with reduced in-hospital mortality, it resulted in a significant increase in bleeding complications.[10] Therefore, it is unclear whether clopidogrel can be substituted with novel oral $P2Y_{12}$ receptor inhibitors in patients with STEMI undergoing PCI; moreover, the optimal duration of DAPT and balance between benefits and risks are uncertain.

Patients with STEMI undergoing PCI are at a high risk of becoming ischemic, and prolonging the duration of DAPT might reduce the incidence of ischemic events, albeit

simultaneously increasing the risk of bleeding. A recently published meta-analysis showed that an extended DAPT duration was not associated with a difference in the risk of all-cause and cardiovascular death compared with short DAPT duration.[11] Furthermore, another earlier meta-analysis on DAPT duration after a drug-eluting stent implantation reported that all-cause mortality was numerically higher with longer DAPT, albeit without statistical significance. Prolonging DAPT requires a careful evaluation, taking into account ischemic and bleeding outcomes or events.[12]

Available studies also have some limitations as almost all trials included in these studies assessed clopidogrel itself; thus, conclusions on the association between treatment with other $P2Y_{12}$ receptor antagonists and mortality cannot be drawn. Therefore, we aimed to investigate the impact of novel oral $P2Y_{12}$ receptor inhibitors on the risk of ischemia and bleeding. In addition, we sought to evaluate the efficacy and safety of shorter DAPT (S-DAPT: 1–3 months) versus longer DAPT (L-DAPT: 12 months or more) for novel oral $P2Y_{12}$ receptor inhibitors in patients with STEMI undergoing PCI, particularly focusing on the incidence rate of all-cause death and bleeding.

METHODS

Data Sources, Search Strategy, and Selection Criteria

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1). To identify all eligible randomized controlled trials (RCTs) of novel oral $P2Y_{12}$ inhibitors versus clopidogrel undertaken during the treatment of patients with STEMI undergoing PCI, we performed a systematic search, without language restrictions, on PubMed, Embase, Cochrane, CNKI, VIP, and WanFang Data databases from January 1980 to February 2016. The following keywords were used: ("ticagrelor" OR "AZD6140" OR "Brilique" OR "Brilinta" OR "prasugrel" OR "CS-747" OR "LY 640315" OR "$P2Y_{12}$ receptor inhibitor") AND ("clopidogrel" OR "plavix") AND ("ST-elevation myocardial infarction" OR "STEMI" OR "myocardial infarction") AND ("percutaneous coronary intervention" OR "PCI") as search terms (Fig. 1 for search strategy). We also conducted a manual search of the reference lists of studies, reviews, and pertinent meta-analyses on this topic.

The literature search was independently undertaken by 2 authors (Q.X. and C.L.) using a standardized approach. Any inconsistencies between these two authors were settled by the primary author (J.J.S.) until a consensus was reached. The studies were included if they met the following inclusion criteria: (1) RCTs that compared novel oral $P2Y_{12}$ receptor inhibitors (prasugrel or ticagrelor) with clopidogrel in patients with STEMI undergoing PCI, (2) the studies reported on ischemic and/or bleeding outcomes, (3) the study was associated with DAPT, and (4) the study included outcomes measured during follow-up time $\geq$1 month. The primary efficacy endpoint was all-cause death and interest efficacy outcomes that included the following: MI (as defined by the American College of Cardiology/American Heart Association definitions[13]), stroke, and stent thrombosis (defined according to the Academic Research Consortium definitions[14]). The composite endpoint of major adverse cardiac events (MACE) used the definitions of the trials concerned (Table 1). The primary safety endpoint was the rate of major bleeding and major/minor bleeding [defined according to the "Thrombolysis in Myocardial Infarction" (TIMI) group]. Studies that met the following criteria were excluded: (1) repeated publication; (2) the original data were incomplete, unable to obtain the relevant data by contacting authors; (3) review or case reports; (4) triple antiplatelet therapy (eg, cilostazol, warfarin, etc); (5) using fibrinolytic drugs before randomized treatment, and (6) the application of other anticoagulant drugs before PCI.

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#1   ticagrelor OR AZD6140 OR Brilique (TM) OR Brilinta (TM)
#2   prasugrel OR CS-747 OR LY 640315
#3   P2Y12 receptor inhibitor
#4   clopidogrel OR plavix
#5   ST elevation myocardial infarction OR STEMI OR myocardial infarction
#6   percutaneous coronary intervention OR PCI
#7   (#1 OR #2 OR #3) AND #4 AND (#5 AND #6)
#8   randomized controlled trials
#9   controlled clinical trial
#10  randomized
#11  #8 OR #9 OR #10
#12  #7 AND #11
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FIGURE 1. Search strategy for PubMed.

Data Extraction and Quality Assessment

Independent data selection, extraction, and evaluation by the 2 researchers (Q.X. and C.L.) were designed in accordance with the inclusion and exclusion criteria. Disparities between investigators regarding the inclusion of each trial were resolved by a third independent investigator (J.J.S.). The following details were recorded for each study: author, year of publication, study name, exclusion criteria, country, number, sex, mean age, intervention, concomitant antiplatelet medication, and doses of antiplatelet agents. Clinical characteristics including clinical outcomes, diabetes, previous MI, previous stroke, as well as the length of follow-up and stent type were also extracted. The methodological quality of the included studies was evaluated by the Cochrane system evaluation manual 5.1.0 and the GRADE guidelines on RCT bias risk assessment tools.[15]

Statistical Analysis

We first conducted a global meta-analysis by using studies involving prasugrel versus clopidogrel subgroup and ticagrelor versus clopidogrel subgroup including all patients with STEMI undergoing PCI. Subsequently, we examined the relationship between the duration of DAPT and the risk of the endpoint. A subgroup meta-analysis was

TABLE 1. Basic Characteristics of the Studies

Trial Name and Year	n	Mean Age	Male (%)	DM (%)	Previous MI (%)	Previous Stroke (%)	Stent Type (%)	Follow-up, mo
Longer DAPT (L-DAPT: 12 mo or more)								
TRITON-TIMI 38, 2009[31]	2438	59	77	17	10	3	BMS (50) DES (45)	1 15
AMIS-Plus, 2015[10]	4602	61	80	16	13	2.7	DES (80)	12
PLATO, 2010[6]	7544	59	76	19	13	3	BMS (78) DES (21)	12
INFUSE-AMI Trial, 2014[23]	452	58	79	10	2	2.4	NA	12
MULTIPRAC Trial, 2015[24]	1260	57	78	13	11	3.5	BMS (54)	12
Shorter DAPT (S-DAPT: 1–3 mo)								
ETAMI Trial, 2015[30]	62	59	68	19	9	NA	DES (89)	1
ATACS-registry, 2015[32]	1820	58	70	18	17	2	DES (48)	1
Que Liang, 2014[28]	60	59	74	13	10	NA	NA	3
Da-qing Song, 2015[27]	112	58	74	15	NA	NA	NA	1
Ji Xu, 2015[26]	113	70	61	29	8	NA	NA	1
Da-yi Liu, 2014[25]	160	68	57	18	7	NA	BMS (30) DES (32)	1
Xiao-dong Qian, 2014[29]	109	65	69	17	NA	NA	NA	1

		Interventions					
Trial Name and Year	Country (%)	Aspirin (LD/MD), mg	New $P2Y_{12}$ (LD/MD), mg	Clopidogrel (LD/MD), mg	Drug Combination (%)	Primary Endpoint	MACE Definition
Longer DAPT (L-DAPT: 12 mo or more)							
TRITON-TIMI 38, 2009[31]	America	325 or 500/75-162	60/10 Qd (P*)	300/75 Qd	Heparin (73) GPI (64)	①②③④⑤⑥	②③④
AMIS-Plus, 2015[10]	Switzerland	300/100	60/10 Qd (P)	300/75 Qd	GPI (21) Heparin (76)	①②③④⑥	②③④
PLATO, 2010[6]	America Asian (6.7)	325/325 Qd	180/90 Bid (T*)	300/75 Qd	GPI (35) Heparin (66)	①②③④⑤⑥	②③④
INFUSE-AMI Trial, 2014[23]	America	325/100	60/10 Qd (P)	600/75 Qd	Bivalirudin (100)	①③④⑤⑥	②③④
MULTIPRAC Trial, 2015[24]	European	325/100	60/10 Qd (P)	600/75 Qd	GPI (32) Heparin (45)	①②③④⑤⑥	②③④
Shorter DAPT (S-DAPT: 1–3 mo)							
ETAMI Trial, 2015[30]	France, Germany	300/100	60/10 Qd (P)	600/75 Qd	Heparin (90) GPI (12)	①②③④⑥	②③④
ATACS-registry, 2015[32]	Germany	300/100	60/10 Qd (P)	600/75 Qd	Heparin (86)	①②③④⑥	②③④
Que Liang, 2014[28]	China	300/100 Qd	180/90 Bid (T)	600/75 Qd	LMWH (NA)	①②③⑥	②③④
Da-qing Song, 2015[27]	China	300/100 Qd	180/90 Bid (T)	600/75 Qd	NA	①⑥	②③④
Ji Xu, 2015[26]	China	300/100 Qd	180/90 Bid (T)	300/75 Qd	LMWH (NA)	①⑥	②③④⑤
Da-yi Liu, 2014[25]	China	300/100 Qd	180/90 Bid (T)	600/75 Qd	Heparin (72) LMWH (29)	①②③④⑤⑥	②③④
Xiao-dong Qian, 2014[29]	China	300/100 Qd	180/90 Bid (T)	600/75 Qd	Enoxaparin (100)	①②⑤⑥	②③④⑤

DM, diabetes mellitus; GPI, GPIIb/IIIa Inhibitors; LD, loading dose; LMWH, low-molecular weight heparin; MD, maintenance dose; NA, not available; P*, prasugrel; primary end-point: ①, MACE; ②, MI; ③, cardiovascular death; ④, stroke; ⑤, stent thrombosis; ⑥, major bleeding; T*, ticagrelor.

performed, restricting the analyses to the S-DAPT group and L-DAPT group. In addition, the relative risk ratio (RRR) and the corresponding 95% confidence intervals (CIs) were estimated using specific RRs and 95% CIs after considering the duration of long-and short-term treatment. Finally, a subgroup analysis of ticagrelor in Chinese patients with STEMI undergoing PCI was performed. The results of all trials were pooled using a random model to minimize heterogeneity between groups and confirmed by a fixed-effects model to avoid small trials being overly weighty. The reported event frequencies were used to calculate risk ratios (RR) with 95% CI in each study. Heterogeneity between trials was investigated using the Q statistic, and we considered $P < 0.10$ as indicative of significant heterogeneity. We also performed a sensitivity analysis by removing each individual study from the meta-analysis and used qualitative Egger's[16] or Begg's[17] tests to check for potential publication bias. All reported P values are 2-sided, and $P < 0.05$ was considered statistically significant for all included studies. Statistical analysis was performed using Review Manager 5.3 software.

RESULTS

Literature Search

A flowchart of the meta-analysis is shown in Figure 2. We found 291 citations in our initial electronic search, of which 45 duplicate results were eliminated and an additional 229 irrelevant articles were excluded. A total of 17 potentially eligible studies were reviewed and detailed evaluations were made. Among these, 5 trials were excluded because it was found that they did not meet the inclusion criteria after the full-texts were read (2 compared DAPT with triple antiplatelet therapy[18,19]; 1 trial had an inconsistent outcome[20]; and 2 trials were non-STEMI studies).[21,22] Finally, 12 RCTs[6,10,23–32] were included in the final meta-analysis. A manual search of the reference lists of these studies did not yield any new eligible studies. The general characteristics of the included trials are presented in Table 1.

Study Characteristics

A total of 18,732 patients from 12 RCTs were included in our analysis. Of these, 9, 498 patients were randomized to novel oral $P2Y_{12}$ receptor inhibitors (prasugrel: 6 RCTs[10,23,24,30–32] with 5,467 patients; ticagrelor: 6 RCTs[6,25–29] with 4,031 patients) treatment, whereas 9,234 patients were randomized to clopidogrel treatment. Two studies were conducted in America,[23,31] 4 in Europe,[10,24,30,32] and 5 in China[25–29]; the PLATO study included 6.7% Asians and the rest were Americans.[6] Clopidogrel loading doses varied between 300[6,10,26,31] and 600 mg.[23–25,27–30,32] The follow-up period for the studies was more than 1 month. The methodological quality of the included studies was evaluated in Table 2.

Novel $P2Y_{12}$ Inhibitors Versus Clopidogrel in Patients With STEMI Undergoing PCI for Global Analysis

The global analysis included all studies. Novel oral $P2Y_{12}$ receptor inhibitors decreased death by 34% from 4.12% to 2.70% (pooled RR: 0.66, 95% CI, 0.54–0.81, $P < 0.0001$) and stent thrombosis (ST) by 47% from 1.90% to 1.01% (pooled RR: 0.59, 95% CI, 0.44–0.81, $P = 0.0009$) than that of clopidogrel. Similarly, MI and MACE were also significantly decreased by 24% (3.73% vs. 2.85%, pooled RR: 0.82, 95% CI, 0.70–0.96, $P = 0.01$) and 24% (7.89% vs. 5.98%, pooled RR: 0.69, 95% CI, 0.57–0.84, $P = 0.0003$), respectively. There was no difference in stroke (pooled RR: 1.28, 95% CI, 0.94–1.74, $P = 0.12$), major bleeding (pooled RR: 1.15, 95% CI, 0.74–1.78, $P = 0.55$), and major/minor bleeding (pooled RR: 1.10, 95% CI, 0.99–1.22, $P = 0.08$) between the novel oral $P2Y_{12}$ inhibitor group and the clopidogrel group. In addition, both prasugrel and ticagrelor could significantly decrease death, MACE, and stent thrombosis than clopidogrel, without increasing major bleeding and major/minor bleeding in our prasugrel versus clopidogrel subgroup and ticagrelor versus clopidogrel subgroup, respectively. All results are shown in Table 3.

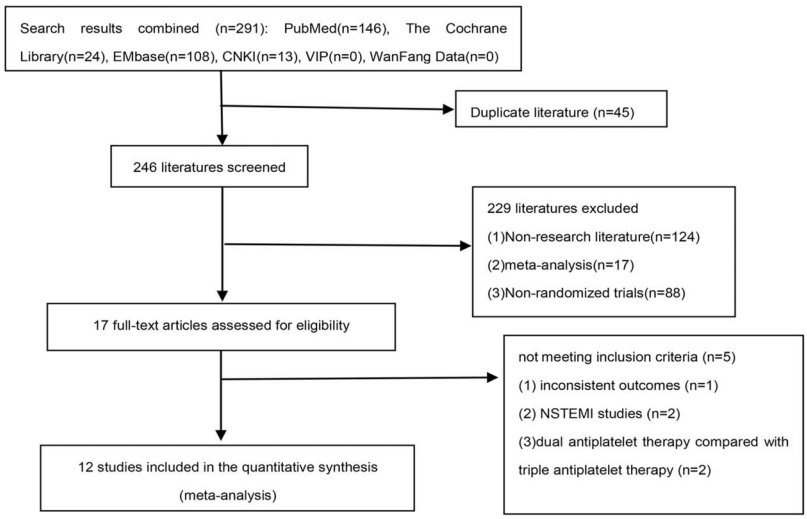

FIGURE 2. Flowchart of study selection.

TABLE 2. Quality Scales for Included Trials

Trial Name and Year	Random Sequence	Allocation Conceal	Blinding		Incomplete Outcome Data (Lost or Quit)	Selective Reporting	Other Bias
			Researcher Subject	Outcome Assessment			
TRITON-TIMI 38, 2009[31]	Clear	Unclear	Double-blind	Clear	Report	None	Unclear
AMIS Plus, 2015[10]	Unclear	Unclear	Open-label	Unclear	Report	None	Unclear
ETAMI Trial, 2015[30]	Clear	Clear	Double-blind	Unclear	Report	None	Unclear
INFUSE-AMI Trial, 2014[23]	Clear	Clear	Open-label	Clear	Report	None	Unclear
MULTIPRAC Trial, 2015[24]	Unclear	Unclear	Open-label	Unclear	Report	None	Unclear
ATACS-registry, 2015[32]	Unclear	Unclear	Open-label	Clear	Report	None	Unclear
PLATO, 2010[6]	Clear	Clear	Double-blind	Clear	Report	None	Explanation
Que Liang, 2014[28]	Unclear	Unclear	Unclear	Unclear	Report	None	Unclear
Daqing Song, 2015[27]	Clear	Clear	Unclear	Unclear	Report	None	Unclear
Ji Xu, 2015[26]	Clear	Clear	Unclear	Unclear	report	None	Unclear
Dayi Liu, 2014[25]	Unclear	Unclear	Open-label	Unclear	Report	None	Unclear
Xiaod Qian, 2014[29]	Unclear	Unclear	Unclear	Unclear	Report	None	Unclear

Potential evidence of heterogeneity was observed in MACE (I^2 = 35%, P = 0.11) and major bleeding (I^2 = 45%, P = 0.10). As a result, a sensitivity analysis was conducted, and after each study was sequentially excluded from the pooled analysis, the conclusion was not affected. All results were confirmed by a fixed-effects model.

Taking into account the effect of the duration of DAPT, we conducted a subgroup analysis for different periods. In our study, through a systematic screening of the literature, we found that this study focused on short-term (1–3 months) and long-term (12 or more months) interventions for DAPT, without reporting mid-term (3–12 months) interventions. The follow-up period of 5 RCTs was 12–15 months, which was defined as longer DAPT (L-DAPT).[6,10,23,24,31] In these trials, the average patient age was 58 years, and the prevalence of diabetes mellitus and MI was 24% and 13%, respectively. Moreover, 8 RCTs that assessed the efficacy and safety during 1–3 months were defined as shorter DAPT (S-DAPT).[25–32] Of these, the average patient age was 63 years, and the prevalence of diabetes mellitus and MI was 18% and 9%, respectively. It should be noted that The TRITON-TIMI 38 study reported the efficacy and safety of DAPT outcome for 1 and 15 months. All results are shown in Figures 3–9.

Novel $P2Y_{12}$ Inhibitors Versus Clopidogrel in Patients With STEMI Undergoing PCI in the L-DAPT Subgroup

This analysis included 5 RCTs[6,10,23,24,31] with a total of 16, 296 patients (n = 8243 in the novel oral $P2Y_{12}$ inhibitor group vs. n = 8053 in the clopidogrel group). Novel oral $P2Y_{12}$ inhibitors could significantly decrease death by 32% from 4.18% to 2.82% (pooled RR: 0.65, 95% CI, 0.47–0.89, P = 0.007) than clopidogrel. Similarly, a significant 44% reduction in ST from 1.86% to 1.04% (pooled RR: 0.61, 95% CI, 0.45–0.84, P = 0.002) was observed. Furthermore, the novel oral $P2Y_{12}$ inhibitors reduced MI (3.20% vs. 4.00%, pooled RR: 0.84, 95% CI, 0.72–0.99, P = 0.04) and MACE (6.49% vs. 8.33%, pooled RR: 0.76, 95% CI, 0.60–0.95, P = 0.02). There was no difference in stroke (P = 0.84), major bleeding (P = 0.63), and major/minor bleeding (P = 0.40) between the 2 groups.

Heterogeneity was observed in the magnitude of the effect across the trials (I^2 = 61%, P = 0.04 for MACE; I^2 = 49%, P = 0.10 for death; I^2 = 59%, P = 0.05 for stroke). According to sensitivity analysis, when we excluded the INFUSE-AMI Trial,[23] the heterogeneity decreased

TABLE 3. The Results for Novel Oral P2Y12 Inhibitors Compared to Clopidogrel in Patients With STEMI Undergoing PCI

End-Point	Novel oral $P2Y_{12}$ Versus Clopidogrel		Prasugrel Versus Clopidogrel		Ticagrelor Versus Clopidogrel	
	RR 95% CI	*P*	RR 95% CI	*P*	RR 95% CI	*P*
MACE	0.69 (0.57–0.84)	0.0003	0.71 (0.57–0.89)	0.002	0.49 (0.27–0.89)	0.02
MI	0.82 (0.70–0.96)	0.01	0.90 (0.69–1.16)	0.41	0.77 (0.63–0.94)	0.01
Death	0.66 (0.54–0.81)	<0.0001	0.56 (0.43–0.73)	<0.0001	0.80 (0.66–0.98)	0.03
Stroke	1.28 (0.94–1.74)	0.12	1.00 (0.62–1.60)	1.00	1.54 (1.03–2.32)	0.04
Stent thrombosis	0.59 (0.44–0.81)	0.0009	0.53 (0.30–0.95)	0.03	0.62 (0.43–0.89)	0.01
Major bleeding	1.15 (0.74–1.78)	0.55	1.54 (0.64–3.71)	0.34	0.98 (0.84–1.14)	0.78
Major/minor bleeding	1.10 (0.99–1.22)	0.08	1.12 (0.86–1.47)	0.40	1.07 (0.95–1.22)	0.25

RR, risk ratio.

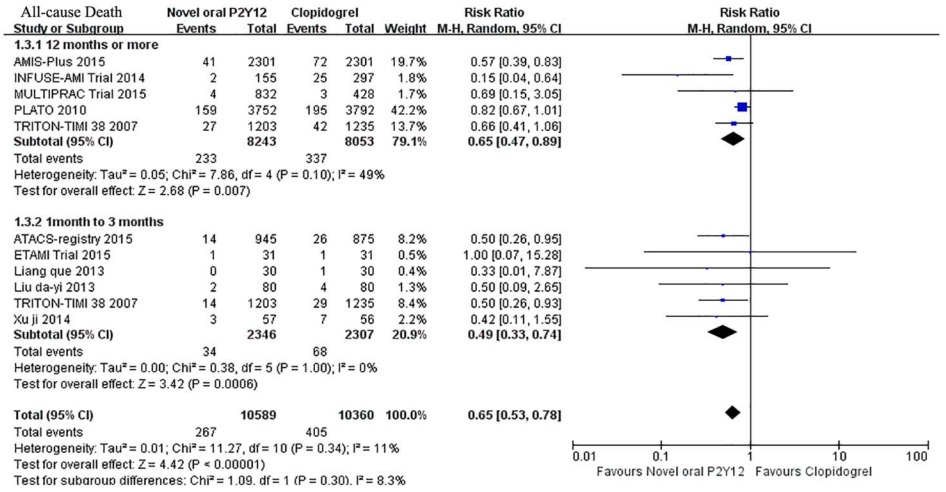

FIGURE 3. All-cause death comparisons: novel oral $P2Y_{12}$ inhibitors compared with clopidogrel in patients with STEMI undergoing PCI.

significantly (I^2 = 0%, P = 0.53 for MACE; I^2 = 4%, P = 0.37 for death; I^2 = 2%, P = 0.38 for stroke). It might indicate that there was a large heterogeneity between the INFUSE-AMI Trial and other RCTs. In the INFUSE-AMI trial, all patients were treated with bivalirudin and then randomized to intralesional abciximab or placebo. Bivalirudin is an anticoagulant, and abciximab is an antiplatelet drug. These might have contributed to affect the ischemic events, leading to the generation of heterogeneity. After this exclusion, we could conclude that novel oral $P2Y_{12}$ inhibitors significantly decreased MACE (pooled RR: 0.84, 95% CI, 0.76–0.94, P = 0.003), stent thrombosis (pooled RR: 0.63, 95% CI, 0.46–0.86, P = 0.003), and death (pooled RR: 0.74, 95% CI, 0.62–0.88, P = 0.0008) than clopidogrel. The results of stroke (pooled RR: 1.31, 95% CI, 0.95–1.81, P = 0.10), major bleeding (pooled RR: 1.02, 95% CI, 0.78–1.35, P = 0.86), and major/minor bleeding (pooled RR: 1.08, 95% CI, 0.87–1.34, P = 0.47) were not affected. The result of MI did not change.

Novel $P2Y_{12}$ Inhibitors Versus Clopidogrel in Patients With STEMI Undergoing PCI in the S-DAPT Subgroup

In this analysis, 4874 patients with STEMI undergoing PCI were included from 8 studies.[25–32] The results showed that novel $P2Y_{12}$ inhibitors had a greater anti-ischemic effect than that of clopidogrel, with a significant reduction of 51% in death (1.44% vs. 2.94%, pooled RR: 0.49, 95% CI, 0.33–0.74, P = 0.0006), 63% in ST (0.86% vs. 2.38%, pooled RR: 0.40, 95% CI, 0.21–0.75, P = 0.004), and 37% in MACE (4.47% vs. 7.16%, pooled RR: 0.56, 95% CI, 0.40–0.79, P = 0.0009). However, novel $P2Y_{12}$ inhibitors increased the major/minor bleeding by 11% (from 1.69% to 2.19%), although it was not statistically significant (P = 0.37). There was no difference in MI (P = 0.10), stroke (P = 0.25), and major bleeding (P = 0.96) between the 2 groups. All results were confirmed by a fixed-effects model. No heterogeneity was observed in the analysis of each endpoint ($P > 0.28$ in all cases). Moreover, when we sequentially excluded each study from all the pooled analyses, the results were not affected.

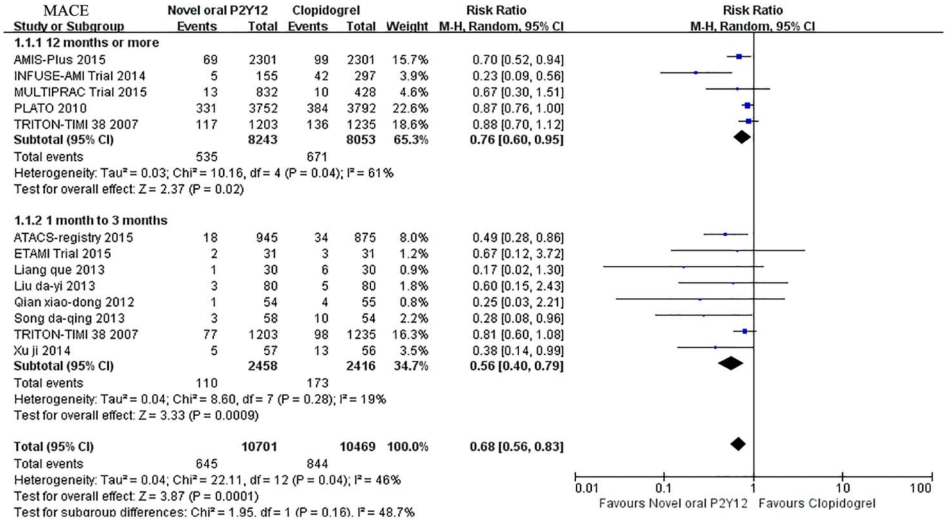

FIGURE 4. MACE comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

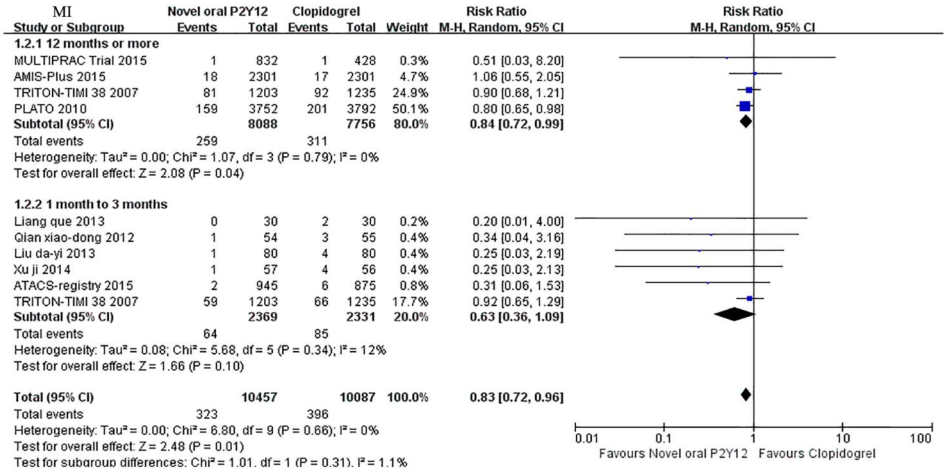

FIGURE 5. MI comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

In addition, we performed a subgroup analysis for ticagrelor versus clopidogrel in Chinese patients with STEMI undergoing PCI. The analysis included 5 studies,[25–29] accounting for 554 Chinese patients (ticagrelor for 279 patients and clopidogrel for 275 patients). The ticagrelor group had a moderate reduction in MACE (3.94% vs. 11.6%, pooled RR: 0.35, 95% CI, 0.18–0.68, $P = 0.002$), and a modest reduction in MI (1.35% vs. 5.88%, pooled RR: 0.26, 95% CI, 0.08–0.84, $P = 0.02$) than that of the clopidogrel group. Moreover, ticagrelor resulted in numerically improved ST ($P = 0.08$) and mortality ($P = 0.10$), but had a greater risk of bleeding ($P = 0.08$) than clopidogrel, although the difference was statistically insignificant. The risk of dyspnea in the ticagrelor group (33/225, 14.6%) was significantly higher than in the clopidogrel group (13/220, 5.9%) ($P = 0.004$). There were no differences regarding the risk of stroke ($P = 0.66$) and bradycardia ($P = 0.44$) between the 2 groups. All results were confirmed by a fixed-effects model. No heterogeneity was observed in evaluated endpoints ($P > 0.70$, $I^2 = 0\%$ in all case). Moreover, when we sequentially excluded each study from all the pooled analyses, the results were not affected. The results are shown in Table 4.

Relative RR (RRR) of Endpoints Compared L-DAPT With S-DAPT for Novel $P2Y_{12}$ Inhibitors

The Relative RR (RRR) of endpoint for the novel oral $P2Y_{12}$ inhibitors was calculated between L-DAPT and S-DAPT (Table 5). The pooled RRR showed no significant difference ($P > 0.05$) in each endpoint, including death ($P = 0.408$), MACE ($P = 0.233$), MI ($P = 0.633$), stroke ($P = 0.327$), stent thrombosis ($P = 0.245$), and bleeding ($P = 0.810$).

Publication Bias

Review of the funnel plots could not rule out potential publication bias for events such as death, MACE, MI, stroke, ST, and bleeding. Egger's and Begg's tests showed no evidence of publication bias for events such as death (P value for Egger's test: 0.229; P value for Begg's test: 0.210), MACE (P value for Egger's test: 0.071; P value for Begg's test: 0.100), MI (P value for Egger's test: 0.208; P value for Begg's test: 0.251), ST (P value for Egger's test: 0.299; P value for Begg's test: 1.000), and bleeding (P value for Egger's test: 0.329; P value for Begg's test: 0.304). Although Egger's test showed no evidence of publication bias for stroke ($P = 0.164$), Begg's test did ($P = 0.048$) (Fig. 10). The

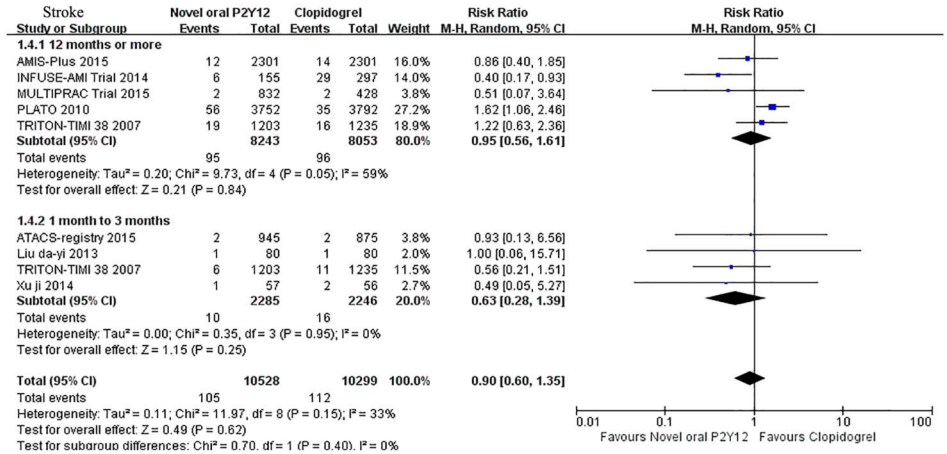

FIGURE 6. Stroke comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

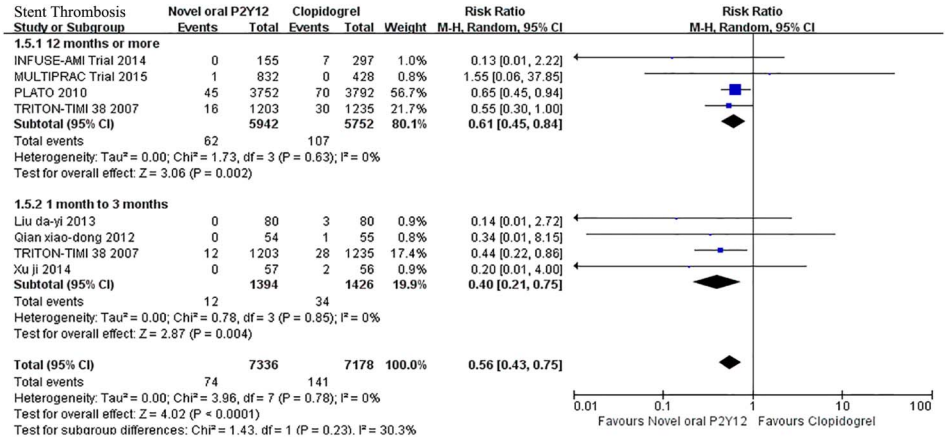

FIGURE 7. Stent thrombosis comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

conclusions were not changed after an adjustment for publication bias was made using the trim and fill method.

DISCUSSION

This study was based on RCTs and explored the efficacy and safety of DAPT with novel oral $P2Y_{12}$ inhibitors against the outcomes of major cardiovascular outcomes. This comprehensive meta-analysis included 18,732 patients from 12 trials. The findings from this study indicated that novel oral $P2Y_{12}$ inhibitors were associated with significant reductions in the incidence of MACE, stent thrombosis, and all-cause death than clopidogrel in patients with STEMI undergoing PCI. Furthermore, subgroup analyses suggested that the administration of novel oral $P2Y_{12}$ inhibitors provided significant reductions in all-cause death, MACE, and stent thrombosis than did clopidogrel without increasing the risk of bleeding in both the S-DAPT and the L-DAPT subgroups; however, a benefit for MI in the L-DAPT group was observed. Identical results were observed in the Chinese patients under ticagrelor treatment, except a slight increase in bleeding. However, when we compared the incidence of endpoints for the novel oral $P2Y_{12}$ inhibitors between S-DAPT and L-DAPT, we observed that L-DAPT might not be associated with a difference in the risk of ischemic events and bleeding compared with S-DAPT.

In a previous meta-analysis that compared novel $P2Y_{12}$ receptor inhibitors with clopidogrel, including oral and intravenous drugs,[33–35] the major limitation could be due to the difference in drug characteristics that resulted in heterogeneity. Others compared novel oral $P2Y_{12}$ inhibitors with clopidogrel in ACS or PCI,[35–39] wherein a meta-analysis of patients without STEMI undergoing PCI[40] was conducted. At present, specific meta-analyses on novel oral $P2Y_{12}$ inhibitors in patients with STEMI undergoing PCI are limited. However, there are 2 articles that focused on the duration of DAPT[11,12] and included trials that assessed clopidogrel without evaluating the novel oral $P2Y_{12}$ inhibitors. In addition, the results of previous meta-analyses were somewhat controversial. The meta-analysis[33] showed that novel $P2Y_{12}$ inhibitors decreased all-cause mortality and major ischemic events, without significant increases in major bleeding in PCI patients. However, a recent meta-analysis[40] indicated that newer oral $P2Y_{12}$ inhibitors decreased MACE and MI at the expense of a significant increase in the risk of bleeding. Therefore, we strictly restricted our analysis to trials that met the inclusion criteria, leading to minimum heterogeneity. The efficacy and safety of novel oral $P2Y_{12}$ inhibitors and clopidogrel in patients with STEMI undergoing PCI were

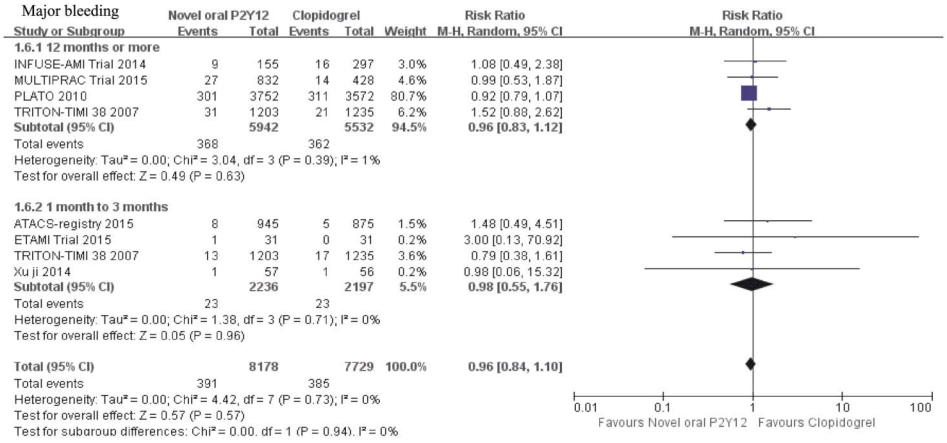

FIGURE 8. Major bleeding comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

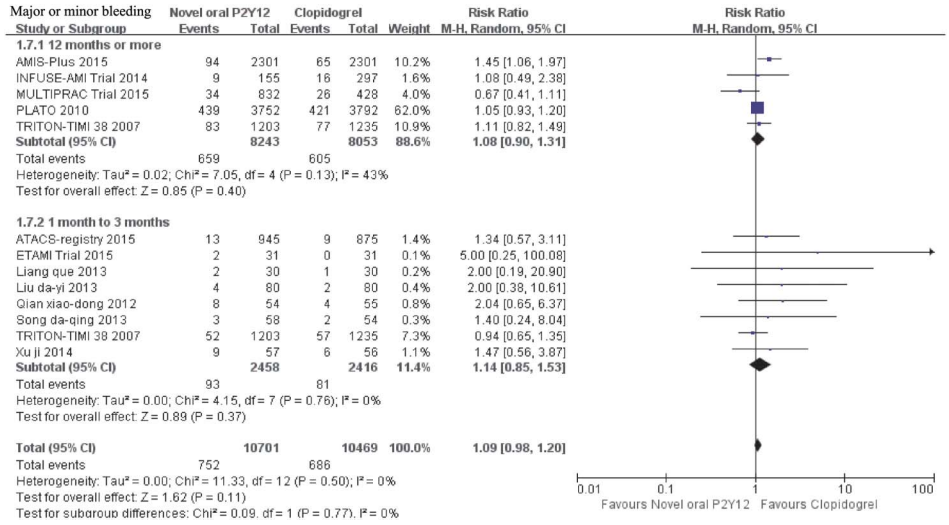

FIGURE 9. Major or minor bleeding comparisons: novel oral $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI undergoing PCI.

compared, and the Relative RR of endpoints for novel oral $P2Y_{12}$ inhibitors was compared among different durations.

Clopidogrel, combined with aspirin, has proved effective in reducing the risk of thrombotic events.[41,42] However, clopidogrel has its own limitations such as delayed onset of action, high individual variability, and moderate platelet inhibition.[43] Therefore, novel oral $P2Y_{12}$ receptor antagonists such as prasugrel and ticagrelor, which compensate for the shortcomings of clopidogrel, were verified by large, double-blind, randomized trials. Our results show that the novel oral antiplatelet agents had more benefits in ischemic events than clopidogrel, particularly in the incidence of MACE, stent thrombosis, and all-cause death, regardless of the overall group, the prasugrel versus clopidogrel subgroup, the ticagrelor versus clopidogrel subgroup, the S-DAPT group, and L-DAPT group, without increasing the risk of bleeding. This benefit might be due to the contribution of novel oral $P2Y_{12}$ inhibitors to the establishment of a better antithrombotic environment within the blood vessels and their ability to effect a more rapid, stronger inhibition of platelet aggregation. Ticagrelor and prasugrel had a rapid onset and offset of antiplatelet action,[44] and marked and consistent inhibitory action on platelet aggregation.[45] In the ONSET/OFFSET trial,[46] the maximum platelet inhibition (~80%) was achieved within 1 hour of ticagrelor administration; the time to peak inhibition of platelet aggregation was 2 hours with ticagrelor compared with 7.8 hours with clopidogrel. Another trial with ticagrelor[6] showed an effective reduction in the incidence of CV death, MI, and stent thrombosis without increasing the risk of bleeding in patients with STEMI undergoing PCI and during a 12-month follow-up after PCI. Furthermore, prasugrel was shown to be effective in the TRITON-TIMI 38 study[9] in reducing the incidence of ischemic events. Our finding further confirmed that the novel $P2Y_{12}$ receptor antagonist significantly reduced ischemic events compared with clopidogrel in patients with STEMI undergoing PCI and theoretically achieved more survival benefits, particularly with regard to MACE, stent thrombosis, and all-cause death. Two large studies[6,31] are included in our global analysis, and their outcomes supported our findings.

Administration of novel oral $P2Y_{12}$ receptor antagonists combined with aspirin is recommended by the current guidelines.[47,48] Clopidogrel is used only as an alternative in case of contraindications in the above-mentioned drugs. However, in Chinese guidelines, novel oral $P2Y_{12}$ oral antiplatelet drugs (ticagrelor and prasugrel) are not recommended as a priority,

TABLE 4. Results for Ticagrelor Compared With Clopidogrel in Chinese Patients With STEMI Undergoing PCI

	Test for Heterogeneity			Test for Overall Effect		
End-Point	**I^2, %**	***P***	**Analysis Model**	**Z**	***P***	**RR 95% CI**
MACE	0	0.85	Random	3.07	0.002	0.35 (0.18–0.68)
MI	0	0.99	Random	2.26	0.02	0.26 (0.08–0.84)
Death	0	0.97	Random	1.66	0.10	0.44 (0.16–1.16)
Stroke	0	0.70	Random	0.45	0.66	0.66 (0.11–4.01)
Stent thrombosis	0	0.92	Random	1.76	0.08	0.21 (0.04–1.20)
Major/minor bleeding	0	0.99	Random	1.72	0.08	1.71 (0.93–3.13)
Dyspnea	0	0.99	Random	2.86	0.004	2.40 (1.32–4.38)
Bradycardia	0	0.99	Random	0.78	0.44	1.49 (0.55–4.07)

RR, risk ratio.

TABLE 5. Incidence of Each End-Point Compared L-DAPT With S-DAPT for Novel Oral $P2Y_{12}$ Inhibitors

End-Point (L-DAPT Versus S-DAPT)	RR 95% CI		RRR	95% CI	*P*
	L-DAPT	S-DAPT			
Death	0.65 (0.47–0.89)	0.49 (0.33–0.74)	1.31	0.69–2.46	0.408
MACE	0.76 (0.60–0.95)	0.56 (0.40–0.79)	1.36	0.82–2.24	0.233
MI	0.84 (0.72–0.99)	0.63 (0.36–1.09)	1.14	0.68–1.91	0.633
Stroke	0.95 (0.56–1.61)	0.63 (0.28–1.39)	1.69	0.59–4.82	0.327
Stent thrombosis	0.61 (0.45–0.84)	0.40 (0.21–0.75)	1.52	0.75–3.11	0.245
Bleeding	1.10 (0.84–1.42)	1.29 (0.86–1.93)	0.94	0.55–1.59	0.810

RR, risk ratio; RRR, relative risk ratio.

mainly because clinical evidence of efficacy of ticagrelor is less substantial in Chinese patients with STEMI undergoing PCI. Therefore, our study conducted subgroup analyses for ticagrelor in Chinese patients. The results showed that ticagrelor could significantly reduce the incidence of MI and MACE, reduce stent thrombosis and mortality, and increase the risk of bleeding and dyspnea compared with clopidogrel. Currently, most studies on the pharmacokinetics of ticagrelor are based on white populations. A study showed that East Asian patients with ACS who underwent PCI and received ticagrelor had higher event rates of primary safety and efficacy endpoints than those who received clopidogrel, albeit not significantly.[49] The average bioavailability of ticagrelor is 1.3-fold higher in Asian populations than in white populations, but dose adjustments based on the basis of race were not sufficient for Asian populations. Therefore, when ticagrelor prevents ischemic events, care should be taken regarding the risk of bleeding.

Subgroup analyses according to the duration of treatment with novel oral $P2Y_{12}$ inhibitors indicated no significant difference between L-DAPT and S-DAPT. The previous REal Safety and Efficacy of a 3-month DAPT after E-ZES implantation (RESET) trial[50] and the OPTIMIZE randomized trial[51] showed that 3 months of DAPT treatment after stent implantation was not inferior to 12 months of DAPT treatment after implantation, in terms of MACE, MI, all-cause death, ST, and major or minor bleeding. Another randomized multicenter trial[52] found that 24 months of clopidogrel therapy was not significantly more effective than 6 months of clopidogrel in reducing the incidence of all-cause death, MI, or cerebrovascular events. Meanwhile, a previously reported meta-analysis of randomized trials[53,54] demonstrated that extending DAPT treatment duration after PCI did not reduce the risk of all-cause death, MI, and MACE, but did increase the risk of major bleeding. In accordance with this meta-analysis and previous trials, our study suggests no difference in adverse cardiovascular events between S-DAPT and L-DAPT treatment with novel oral $P2Y_{12}$ inhibitors, and the risk of bleeding was not increased. However, the meta-analysis and trials described above assessed clopidogrel without evaluating the novel oral $P2Y_{12}$ inhibitors. The difference in bleeding risk might be related to the characteristics of the drugs, in that the novel oral $P2Y_{12}$ inhibitors might contribute to faster, greater, and more consistent therapeutic action than clopidogrel. The results suggest that long-term DAPT with novel oral $P2Y_{12}$ inhibitors might retain a powerful benefit for ischemia, a theory supported by European and US guidelines that recommend a duration of at least 12 months for prasugrel or ticagrelor DAPT.[4,55] The optimal duration of DAPT remains uncertain, however, and a longer duration of treatment may be required. To date, one randomized control trial[56] has compared 12-month DAPT with 30-month DAPT for novel oral $P2Y_{12}$ inhibitors and showed that continuing DAPT with prasugrel and aspirin for 30 months was associated with lower rates of MACE, driven largely by fewer spontaneous and ST-related MI with no apparent increase in severe bleeding. Therefore, assessment of the optimum duration for DAPT using novel oral $P2Y_{12}$ inhibitors in patients with STEMI undergoing PCI has been mainly concerned with balancing the incidence of ischemic complications (such as MI, stent thrombosis, and stroke) with bleeding complications.

Two strengths of our study should be highlighted. First, only prospective studies were included, which avoids selection and recall bias. Second, we strictly limited the condition of the disease, and divided the group according to the follow-up time, which can effectively reduce the heterogeneity between studies.

There are several limitations of our study that should be considered. The main limitation of the study is the inclusion of some small-scale original studies. Although medium and large-scale studies were included and the number of patients increased, the small-scale studies could still introduce bias. Therefore, larger and higher-quality RCTs are required to confirm our findings in the future. The second is a lack of patient-level data. Patient-level data can be used as a basis for identifying ischemic benefits and the risk of bleeding during different durations of DAPT. In particular, not all studies reported on the use of stent type; different stent types have been related to the safety and efficacy of endpoints in patients undergoing PCI.[57] Third, the bias may be introduced by the different follow-up times. Most of the clinical effects focused on short-term studies such that the lower incidence of endpoints might be accounted for by the lower exposure and shorter follow-up time. Furthermore, all the studies were not conducted with genotypes of clopidogrel for hepatic cytochrome Cyp2C19 gene polymorphism, which is about 25%–30% of the patients taking clopidogrel, reducing protection from clopidogrel in preventing cardiovascular events after PCI.[58] Therefore, it will increase the incidence of endpoint events that can affect the results of our study by introducing bias.

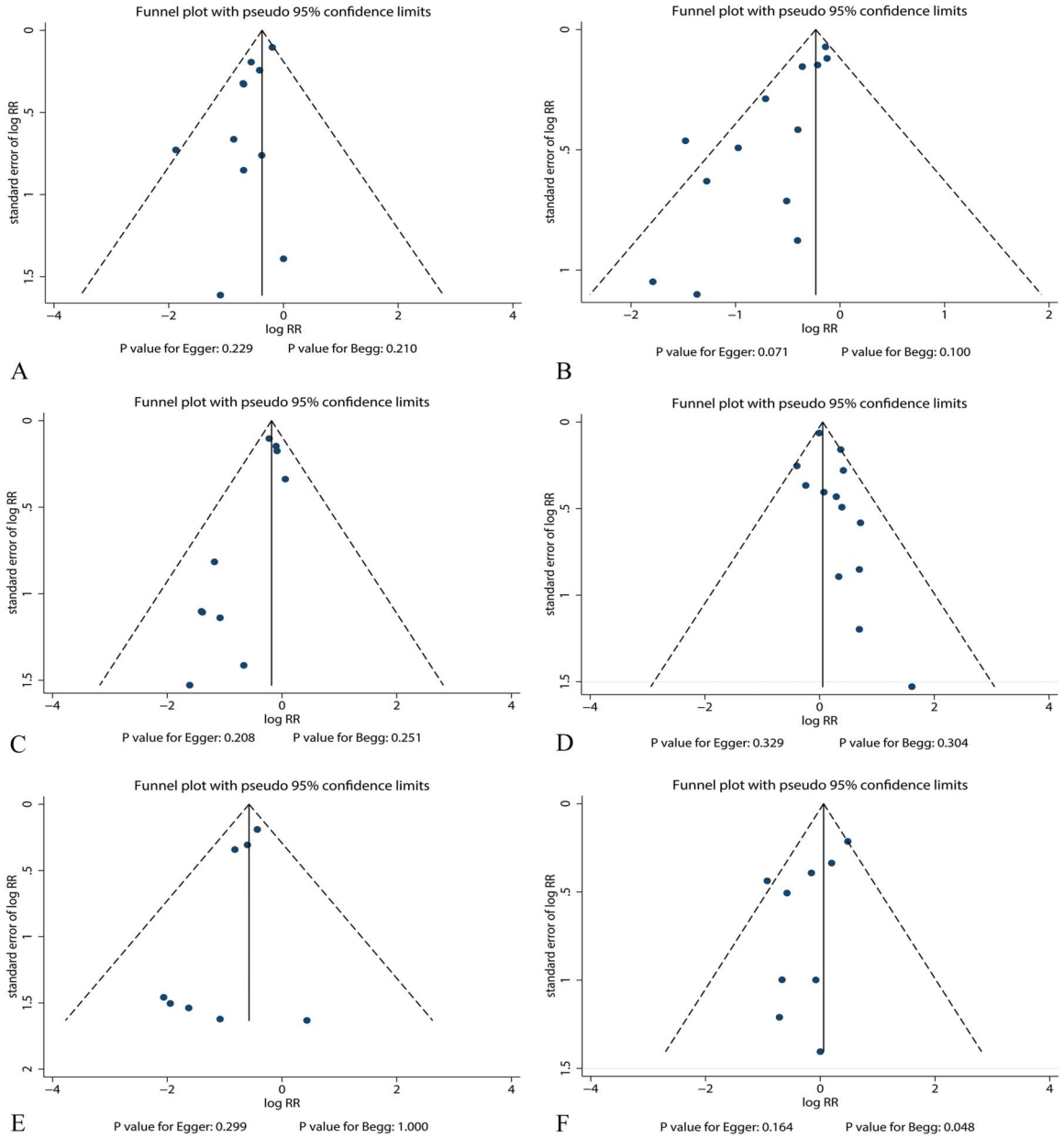

FIGURE 10. Funnel plot with pseudo 95% confidence limits for the risk of endpoints: (A) all-cause death; (B) MACE; (C) MI; (D) major or minor bleeding; (E) stent thrombosis; (F) stroke.

Finally, there was heterogeneity between the studies. Although we tried to strictly limit the inclusion and exclusion criteria to ensure a more homogenous population in our meta-analysis, there was a large difference in protocols, endpoint definitions, and follow-up periods between trials. Each trial might have reported and adjudicated the endpoints with a slight difference.

CONCLUSION

Patients with STEMI undergoing PCI who received novel oral $P2Y_{12}$ inhibitors had significant reductions in the risk of MACE, all-cause death, and stent thrombosis without a significant effect on the risk of bleeding events compared with clopidogrel. However, extended duration of treatment with potential $P2Y_{12}$ inhibitors might be not associated with the risk of ischemic events and bleeding compared with short-duration DAPT in patients with STEMI undergoing PCI.

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