

Effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow phenomenon during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis

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Background: Previous studies have shown that ticagrelor is more effective than clopidogrel in platelet inhibition. However, this conclusion remains controversial. Therefore, we performed this meta-analysis to assess the effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow (NRF) during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PPCI).

Materials and methods: Randomized controlled trials and observational studies were reviewed. The retrieval time was limited from inception to October 1, 2017. The retrieved databases included PubMed, Embase, the Cochrane Library, Web of Science, CBM, CNKI, the VIP database, and the Wang Fang database. RevMan 5.3 software was used for data analysis.

Results: Fourteen randomized controlled trials and one observational study, including 4,162 patients, were included. In these articles, 1,521 patients were in the ticagrelor group (180 mg) and 2,641 patients were in the clopidogrel group (600 mg). The meta-analysis showed that compared with clopidogrel group, preoperative loading dose ticagrelor: 1) significantly reduced the incidence of NRF during PPCI (95% confidence interval [CI]: 0.15, 0.39, $P < 0.05$) as well as the level of postoperative corrected thrombolysis in myocardial infarction frame count (95% CI: -8.89 , -6.91 , $P < 0.05$); 2) significantly reduced the incidence of major adverse cardiovascular events during hospitalization, including 30 and 180 days after PPCI (95% CI: 0.41, 0.82, $P < 0.05$; 95% CI: 0.15, 0.46, $P < 0.05$, respectively); and 3) significantly improved thrombolysis in myocardial infarction flow after PPCI (95% CI: 1.40, 2.45, $P < 0.05$). No significant difference was observed in terms of bleeding events within 30 and 180 days after PPCI (95% CI: 0.71, 1.54, $P = 0.82$; 95% CI: 0.81, 3.19, $P = 0.18$, respectively).

Conclusion: Compared with clopidogrel, loading dose ticagrelor effectively reduced both the occurrence of NRF during PPCI and the incidence of major adverse cardiovascular event in patients with ST-segment elevation myocardial infarction undergoing PPCI. Furthermore, it did not increase the risk of bleeding after PPCI.

Keywords: ticagrelor, clopidogrel, primary PCI, no-reflow, meta-analysis

Introduction

Currently, with the improvement in living standards and the changes in diet and living environments, the incidence of coronary heart disease (CHD) has increased.¹ Acute ST-segment elevation myocardial infarction (STEMI), a type of CHD, is a common global disease with a high mortality rate that is caused by a sharp reduction of coronary blood supply from an infarct-related artery (IRA). In general, the blockage, based on unstable coronary atherosclerotic plaque rupture and thrombosis, results in decreased blood flow in the IRA. As a consequence, some cardiac muscle is unable to function properly, and if the myocardium remains ischemic for a few hours, it becomes necrotic. Thus, recovering the blood flow in the IRA and performing revascularization as soon as possible are the most important treatments to improve the prognosis of patients with STEMI. Primary percutaneous coronary intervention (PPCI) is an important means of treating patients with STEMI, so that the IRA can be opened quickly and effectively. In addition, before PPCI, effective antiplatelet therapy is of critical importance in patients with STEMI. The newest European and American guidelines for STEMI both recommend that it is necessary for patients with STEMI undergoing PPCI to take one kind of P2Y₁₂ receptor antagonist combined with aspirin as soon as possible for antiplatelet therapy.

Previous studies have demonstrated that the loading dose ticagrelor, a new P2Y₁₂ receptor antagonist, is more effective and has a faster antiplatelet effect than clopidogrel.^{2,3} This superior antiplatelet effect allows ticagrelor to effectively reduce thrombosis and prevent ischemic events. In addition, the global multicenter, double-blind, randomized controlled PLATO trial suggested that ticagrelor is effective in improving the prognosis of patients with acute coronary syndrome (ACS), and that the same improvement was demonstrated in the subgroup of patients with STEMI in PLTAO trial.⁴

The no-reflow (NRF) phenomenon occurs when, although the revascularization of IRA has been completed, the blood flow of IRA in angiography is still obstructed and cannot restore thrombolysis in myocardial infarction (TIMI) flow 3 (TIMI3), excluding the cause of coronary spasm, dissection, thrombosis, and other external factors. NRF causes myocardium ineffective perfusion and significantly affects the prognosis of patients with STEMI.⁵ Some studies have shown that the incidence of NRF in patients undergoing PPCI is higher than that in patients undergoing selective PCI; this incidence is ~10%–30%, depending on the incomplete statistics.⁶ Although there are many mechanisms that lead to the occurrence of NRF, the predominant cause is that the

debris from fissured or ruptured atherosclerotic plaque during PCI moves downstream and forms a microembolism, which can mechanically block the distal blood vessels.⁷ Therefore, strengthening antiplatelet therapy and reducing the formation of microembolisms may be ways to prevent the occurrence of NRF during PPCI.

Some studies found that the administration of preoperative loading dose ticagrelor can reduce the incidence of NRF during PPCI and effectively improve coronary blood reperfusion.^{8,10–12} However, the conclusions have been inconsistent. The ATLANTIC study reported that prehospital ticagrelor did not improve early coronary reperfusion more than in-hospital ticagrelor did in patients with new STEMI undergoing PPCI.⁹ In addition, some of these trials had small samples, resulting in poor clinical reliability. A few scholars have directly compared the efficacy of ticagrelor to clopidogrel with respect to the incidence of NRF phenomenon during interventions in patients with STEMI undergoing PPCI. Therefore, we performed this meta-analysis to assess the effect of preoperative loading dose ticagrelor and clopidogrel on NRF during interventions in patients with STEMI undergoing PPCI to provide a guide for clinical application.

Materials and methods

Literature search

According to the guidelines of the preferred reporting items for systematic reviews and meta-analyses, two researchers independently searched for published articles investigating the effects of preoperative loading dose ticagrelor and clopidogrel on NRF phenomenon during intervention in patients with STEMI undergoing PPCI. The retrieved databases included PubMed, Embase, the Cochrane Library, Web of Science, CBM, CNKI, the VIP database, and the Wang Fang database. The retrieval time was limited from inception to October 1, 2017. The search was performed using the keywords “(Ticagrelor) and (STEMI) and (no-reflow) and (PPCI)” for all articles available. Relevant keywords related to ticagrelor in combination with MeSH terms and text words (“Brilinta” or “AZD 6140” or “AZD6140”) were used in combination with words related to ST-segment elevation myocardial infarction (“STEMI” or “ST Elevated Myocardial Infarction”) and words related to the NRF phenomenon (“Slow-Flow Phenomenon” or “Slow-Flow” or “Slow Flow Phenomenon”). Articles written in English and Chinese were chosen, and the references of the extracted articles were retrieved. When the same study was reported by multiple journals, we used the most recent article. Because this analysis was based on previously published studies, there was no requirement for ethical approval or patient consent.

Study selection

We identified studies that assessed the effect of preoperative loading dose ticagrelor and clopidogrel on NRF during interventions in patients with STEMI undergoing PPCI. In the literature review, we first read the text and summary to exclude irrelevant literature, and we then read the full text to determine the final studies for inclusion according to the inclusion/exclusion criteria.

Inclusion criteria

1) All patients met the STEMI diagnostic criteria recommended by the newest American College of Cardiology/American Heart Association guideline and underwent PPCI treatment to complete revascularization; 2) the studies were limited to randomized controlled trials (RCTs) and observational studies; 3) patients with chest pain <12 h; 4) the experimental group used ticagrelor 180 mg combined with aspirin for antiplatelet therapy, and the control group used clopidogrel 600 mg combined with aspirin for antiplatelet therapy; 5) the duration of use for each P2Y₁₂ receptor antagonist was limited before PPCI; 6) coronary angiography confirmed the IRA of each patient based on thrombotic infarction, and all patients completed PPCI treatment; 7) patients were older than 18 years; and 8) article provided sufficient data for analysis.

Exclusion criteria

1) Articles with incomplete or erroneous data; 2) patients were allergic to ticagrelor or clopidogrel; 3) patients had a history of recent major bleeding, malignant tumor, pulmonary infarction, serious infections, coagulation dysfunction, platelet abnormalities, or other hemorrhagic blood system diseases; 4) over the past 6 months, patients had a history of cerebral hemorrhage, surgery, or trauma; 5) patients were diagnosed with cardiogenic shock or cardiac function \geq Killip III; 6) patients were suspected of aortic dissection; and 7) dysfunctional patients.

Data extraction

The contents of the retrieved studies that were selected according to the prior search methods were scanned and extracted by two reviewers independently. Homemade data extraction tables were used to extract the data. Then, two reviewers cross-checked the data. If there were any discrepancies, the extracted data were subjected to third-party decision. The extracted data included basic data of the subjects (first author, year of publication, country, mean age, male/female ratio), intervention measure, and observation index. If there was a lack of necessary information in the

article, we made every effort to contact the author and acquire complete data, and we excluded the article if the necessary data remained unavailable.

Statistical analysis

We used Review Manager 5.3 software for data analysis. Odds ratio and mean difference were used as the effect index. Pooled results were presented with 95% confidence intervals (CIs) with two-sided *P*-values. *P*<0.05 indicated that the difference was statistically significant. Heterogeneity of the inclusion study was assessed using the *I*² test to assess the appropriateness of pooling the individual study results. When *I*²<50%, the heterogeneity of the study was considered small; when *I*²>50%, the heterogeneity of the study was considered substantial. Funnel plots were used to investigate the sources of heterogeneity.

Results

We searched the relevant articles that were written in Chinese or English and that were published from inception to October 1, 2017. In total, 14 RCTs and one observational comparative study, including 4,162 patients, were included in our meta-analysis.^{8,10–23} The literature screening process and results are shown in Figure 1. Among these articles, 1,521 patients were placed in the ticagrelor (180 mg) group, and 2,641 patients were placed in the clopidogrel (600 mg) group. The basic information of the included studies is summarized in Table 1.

Literature quality evaluation

Of the 14 RCTs, four articles used a random number table for randomization,^{8,12,16,23} three articles used a closed envelope,^{17,21,22} and others referred to a randomization method but did not describe it clearly.^{10,11,13–15,18,19} The hidden distribution of the 14 articles was low,^{8,10–19,21–23} and seven articles used a single-blind method.^{8,11–13,17,21,22} However, it was unclear whether the other seven articles used a blind method.^{10,14–16,18,19} The 14 articles did not include much incomplete outcome data.^{8,10–19,21–23} The inclusion and exclusion criteria that each article met were described in detail,^{8,10–19,21–23} and the other biases of the 14 articles were low.^{8,10–19,21–23} The literature quality score is shown in Table 2. Detailed data regarding time for loading and PCI are shown in Table 3.

Meta-analysis results

Change in TIMI flow after PPCI

Nine articles, including 3,125 patients, reported the change of coronary TIMI flow of IRA after PPCI.^{8,10,11,13,16,18–21} The fixed effect model meta-analysis result showed that compared with the clopidogrel group, the preoperative loading dose

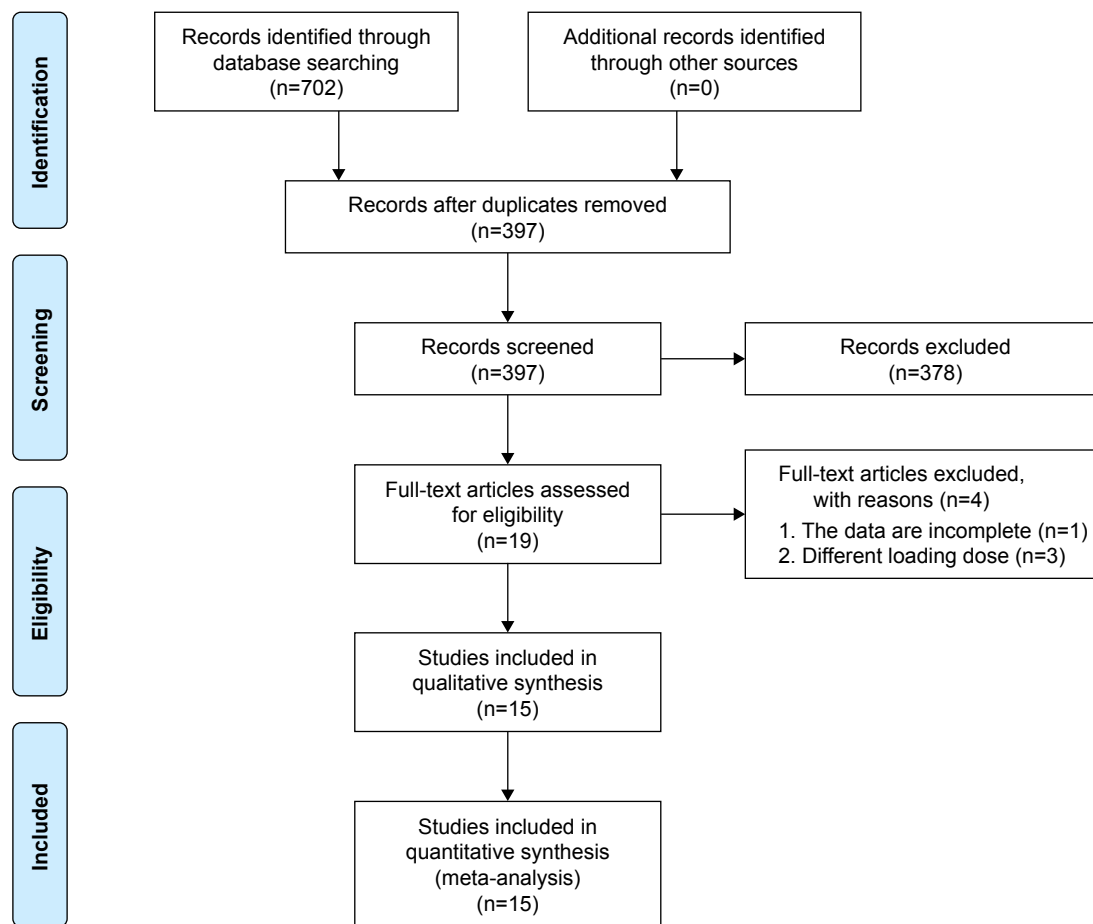


Figure 1 Flowchart of the selection strategy and inclusion/exclusion criteria in the current meta-analysis.

Table 1 Basic information of studies included in the current meta-analysis

Author	Year	Country	Gender (male/female)		Average age (years)	Intervening measures		Outcome measures
			T	C		T	C	
Limin et al ⁹	2016	China	44/14	37/10	55.0±9.5/50.0±11.2	Ticagrelor 180 mg	Clopidogrel 600 mg	①②③④⑤⑥⑦
Zhaohui et al ¹⁰	2015	China	38/22	36/24	56.3±15.2/58.2±14.4	Ticagrelor 180 mg	Clopidogrel 600 mg	①②③④⑤⑦
Zhang et al ¹¹	2015	China	26/12	29/11	57.8±10.3/59.2±11.2	Ticagrelor 180 mg	Clopidogrel 600 mg	①②④⑤
Ningbo et al ¹²	2016	China	52/10	51/14	57.9±12.9/59.7±12.11	Ticagrelor 180 mg	Clopidogrel 600 mg	②⑤⑦
Bing et al ¹³	2015	China	142/51	185/74	61.8±10.9/61.4±11.5	Ticagrelor 180 mg	Clopidogrel 600 mg	①②④⑤
Yujun ¹⁴	2016	China	27/15	29/13	62.1±7.9/61.3±8.1	Ticagrelor 180 mg	Clopidogrel 600 mg	②
Fangcheng and Fang ¹⁵	2015	China	58/49	70/57	54.74±10.93/56.43±11.57	Ticagrelor 180 mg	Clopidogrel 600 mg	②
Ji et al ¹⁶	2015	China	36/21	34/22	71.38±12.16/70.69±12.32	Ticagrelor 180 mg	Clopidogrel 600 mg	①②④⑤
Jing-gang et al ¹⁷	2015	China	36/12	38/10	53.7±10.3/54.6±9.8	Ticagrelor 180 mg	Clopidogrel 600 mg	⑥⑦
Mont'Alverne-Filho et al ¹⁸	2016	Brazil	28/18	30/14	58/58 ^a	Ticagrelor 180 mg	Clopidogrel 600 mg	①
Zhu et al ¹⁹	2015	China	21/16	20/17	59.5±4.63/60.2±4.23	Ticagrelor 180 mg	Clopidogrel 600 mg	①
De et al ²⁰	2015	Denmark	356/135	1,133/399	63.2±12.5/63.9±12.9	Ticagrelor 180 mg	Clopidogrel 600 mg	①④⑤
Winter et al ²¹	2014	Chile	27/7	25/11	55.1±8.3/62.1±10.5	Ticagrelor 180 mg	Clopidogrel 600 mg	①
Tang et al ²²	2016	China	142/58	146/54	64.36±11.409/64.18±11.088	Ticagrelor 180 mg	Clopidogrel 600 mg	⑥⑦
Ming et al ²³	2016	China	26/22	27/21	58.12±9.68/60.74±10.03	Ticagrelor 180 mg	Clopidogrel 600 mg	⑤⑥

Notes: T, ticagrelor group; C, clopidogrel group; ①, thrombolysis in myocardial infarction (TIMI) flow after PPCI; ②, no-reflow phenomenon during PPCI; ③, corrected TIMI frame count (cTFC) after PPCI; ④, bleeding events within 30 days after PPCI; ⑤, major adverse cardiovascular events (MACE) in the hospital/within 30 days after PPCI; ⑥, bleeding events within 180 days after PPCI; ⑦, MACE within 180 days after PPCI. ^aThe age of patients in this article is represented as arithmetic average.

Table 2 Assessment of methodological quality of included studies

Study	Random allocation	Hidden distribution	Blind method	Incomplete outcome data	Selective reporting of results	Other bias	Quality grade
Limin et al ⁸	Random number table	Low	Single-blind	Low	Low	Low	A
Zhaohui et al ¹⁰	Mentioned random	Low	Unclear	Low	Low	Low	B
Zhang et al ¹¹	Mentioned random	Low	Single-blind	Low	Low	Low	A
Ningbo et al ¹²	Random number table	Low	Single-blind	Low	Low	Low	A
Bing et al ¹³	Mentioned random	Low	Single-blind	Low	Low	Low	A
Yujun ¹⁴	Mentioned random	Low	Unclear	Low	Low	Low	B
Fangcheng and Fang ¹⁵	Mentioned random	Low	Unclear	Low	Low	Low	A
Ji et al ¹⁶	Random number table	Low	Unclear	Low	Low	Low	B
Jing-gang et al ¹⁷	Closed envelope	Low	Single-blind	Low	Low	Low	A
Mont'Alverne-Filho et al ¹⁸	Mentioned random	Low	Unclear	Low	Low	Low	A
Zhu et al ¹⁹	Mentioned random	Low	Unclear	Low	Low	Low	A
De et al ²⁰	Nonrandom	Unclear	Unclear	Unclear	Unclear	Unclear	–
Winter et al ²¹	Closed envelope	Low	Single-blind	Low	Low	Low	A
Tang et al ²²	Closed envelope	Low	Single-blind	Low	Low	Low	A
Ming et al ²³	Random number table	Low	Unclear	Low	Low	Low	B

ticagrelor significantly improved the number of patients whose coronary blood flow of IRA restored TIMI3 after PPCI ($I^2=26\%$, 95% CI: 1.40, 2.45, $P<0.05$) (Figure 2).

Incidence of NRF phenomenon during PPCI

Eight articles, including 1,301 patients, reported intraoperative NRF phenomenon during PPCI.^{8,10–16} The fixed effect model meta-analysis showed that compared with the clopidogrel group, preoperative loading dose ticagrelor significantly reduced the incidence of the NRF phenomenon during PPCI ($I^2=0\%$, 95% CI: 0.15, 0.39, $P<0.05$) (Figure 3).

Change in corrected TIMI frame count (cTFC) after PPCI

Four articles, including 422 patients, reported the change of the level of cTFC after PPCI.^{8,10,12,21} The fixed effect model meta-analysis showed that compared with the clopidogrel group, preoperative loading dose ticagrelor significantly reduced the level of cTFC after PPCI ($I^2=69\%$, 95% CI: -9.89 , -6.91 , $P<0.05$) (Figure 4). The heterogeneity of the included articles was substantial ($I^2>50\%$), and funnel plots were used to assess publication bias (Figure 5), indicating that there might be some heterogeneity in these included articles.

Table 3 The detailed information of time about loading and PCI

Study	Transport time (hours)		Time of door to balloon (minutes)		Time of loading to PCI (minutes)		Time of onset to opening of IRA (hours)	
	T	C	T	C	T	C	T	C
Limin et al ⁸	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	6.9±2.1	7.1±1.9
Zhaohui et al ¹⁰	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	7.5±3.1	7.3±2.8
Zhang et al ¹¹	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ningbo et al ¹²	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	7.9±4.7	8.6±4.8
Bing et al ¹³	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	6.3±2.1	6.0±2.3
Yujun ¹⁴	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Fangcheng and Fang ¹⁵	5.68±2.46	6.04±3.31	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ji et al ¹⁶	7.61±1.83	7.42±1.55	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jing-gang et al ¹⁷	4.8±3.5	4.6±3.6	109±39	112±41	Unclear	Unclear	Unclear	Unclear
Mont'Alverne-Filho et al ¹⁸	5.65	6.6	77	78	45	54	Unclear	Unclear
Zhu et al ¹⁹	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
De et al ²⁰	1.18	1.15	Unclear	Unclear	86	100	Unclear	Unclear
Winter et al ²¹	4.4±2.7	4.3±2.6	Unclear	Unclear	35.2±36.4	42.7±29.5	Unclear	Unclear
Tang et al ²²	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ming et al ²³	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Abbreviations: T, ticagrelor group; C, clopidogrel group; IRA, infarct-related artery; PCI, percutaneous coronary intervention.

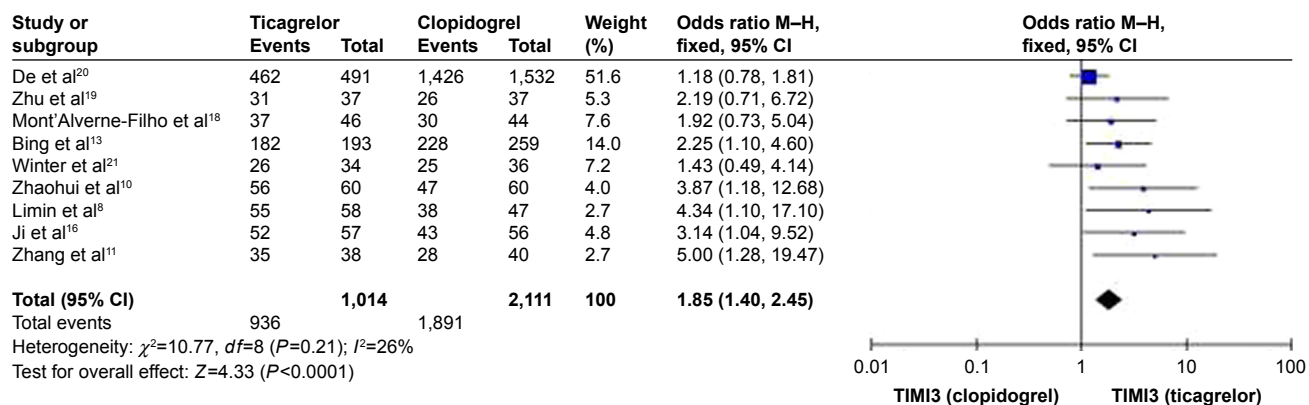


Figure 2 Forest plot of TIMI flow after PPCI.

Abbreviations: TIMI, thrombolysis in myocardial infarction; PPCI, primary percutaneous coronary intervention; CI, confidence interval; TIMI3, TIMI flow 3.

Incidence of major adverse cardiovascular events (MACE) after PPCI

Seven articles, including 2,987 patients, reported the occurrence of MACE in the hospital or within 30 days after PPCI.^{8,10,11,13,16,20,23} Five articles, including 805 patients, reported the occurrence of MACE within 180 days after PPCI.^{8,10,12,17,22} The fixed effect model meta-analysis showed that compared with the clopidogrel group, preoperative loading dose ticagrelor significantly reduced the incidence of MACE within 30 days after PPCI ($I^2=19\%$, 95% CI: 0.41, 0.82, $P<0.05$) (Figure 6) or within 180 days after PPCI ($I^2=0\%$, 95% CI: 0.15, 0.46, $P<0.05$) (Figure 7).

Incidence of bleeding events after PPCI

Six articles, including 2,891 patients, reported the occurrence of bleeding events in the hospital or within 30 days after PPCI.^{8,10,11,13,16,20} Three articles, including 601 patients, reported the occurrence of bleeding events within 180 days after PPCI.^{8,17,22} The fixed effect model meta-analysis showed that compared with the clopidogrel group, preoperative

loading dose ticagrelor group did not show increased incidence of bleeding events, either in 30 days after PPCI ($I^2=25\%$, 95% CI: 0.71, 1.54, $P=0.82$) (Figure 8) or within 180 days after PPCI ($I^2=0\%$, 95% CI: 0.81, 3.19, $P=0.18$) (Figure 9).

Discussion

The most important treatment for acute STEMI is the timely completion of IRA reperfusion. Under conditions of a mature interventional technique and necessary medical equipment, primary PCI is considered the first-choice treatment for patients with STEMI.²⁴ PPCI can quickly and effectively open the IRA and complete IRA reperfusion to avoid myocardial ischemia. After the completion of PPCI, most symptoms related to STEMI can improve immediately, and coronary blood flow can be restored to TIMI3. However, in a small proportion of patients, coronary blood flow continues to exhibit overt obstruction or slow flow despite the successful opening of IRA, after excluding vessel spasm, dissection, and other external causes. This phenomenon is called NRF.

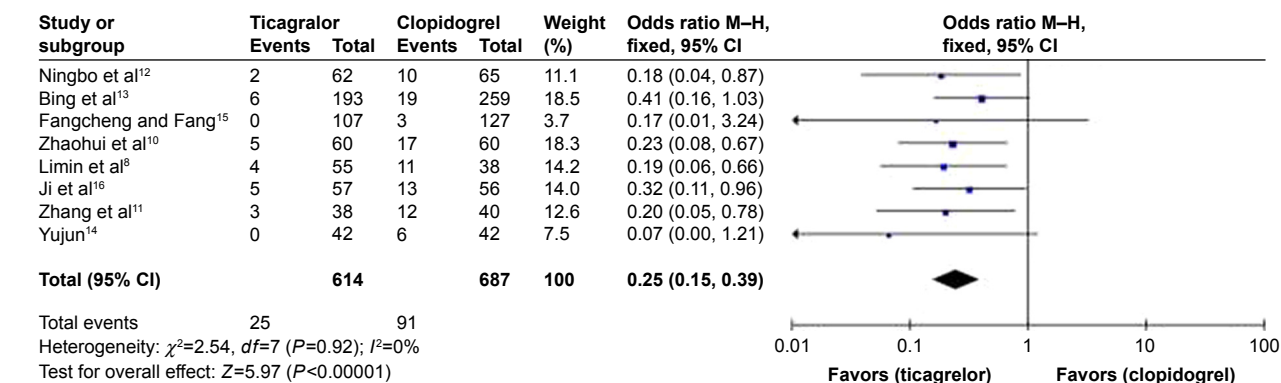


Figure 3 Forest plot of no-reflow phenomenon during PPCI.

Abbreviations: PPCI, primary percutaneous coronary intervention; CI, confidence interval.

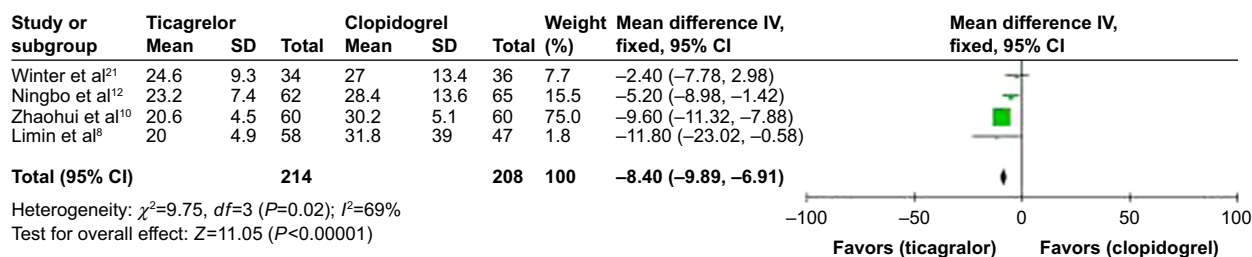


Figure 4 Forest plot of the change of cTFC after PPCI.

Abbreviations: TIMI, thrombolysis in myocardial infarction; PPCI, primary percutaneous coronary intervention; CI, confidence interval; cTFC, corrected TIMI frame count.

Some studies have shown that PPCI is more likely to occur with the NRF phenomenon during intervention, with an incidence of ~10%–30%.²⁵ Simultaneously, compared with patients without NRF phenomenon during PPCI, the mortality of the NRF group was higher at 30 days and 6 months.²⁶ In addition, Ndrepepa et al found that when patients with NRF achieved normal blood flow, their left ventricular ejection fraction was higher than before and that the occurrence of NRF could be used as an independent predictor of death.²⁷ It is generally believed that the main mechanism of NRF is thrombus and plaque debris caused by stenting or balloon dilatation moving downstream, leading to distal vascular mechanical microembolization.²⁸ The treatment of NRF often returned poor results, and prevention is more important than treatment.²⁹ Thus, strengthening dual antiplatelet therapy, which is the preoperative basic treatment of PPCI, may inhibit platelet function and reduce the formation of microembolization by decreasing platelet adhesion to debris. This may be the key treatment for preventing NRF during PPCI. A new P2Y₁₂ receptor inhibitor, ticagrelor, provides better outcomes compared with clopidogrel, as demonstrated in patients with ACS in

the PLATO trial. However, few large clinical trials have investigated the influence of preoperative loading dose ticagrelor on the NRF phenomenon during PPCI in patients with STEMI.

In our current meta-analysis, we found that compared with the clopidogrel group, preoperative loading dose ticagrelor significantly reduced the incidence of the NRF phenomenon during PPCI ($\chi^2=2.54$, $I^2=0\%$, 95% CI: 0.15, 0.39, $P<0.05$), suggesting that preoperative loading dose ticagrelor may reduce the formation of microembolization resulting in NRF, improving reperfusion more effectively than did loading dose clopidogrel. This effect may occur via more potent platelet inhibition or other effects of ticagrelor that could provide potential benefits in patients with ACSs.

Clopidogrel is a thiophene pyridine antiplatelet active drug precursor that requires the metabolic activation of liver enzymes to produce active drugs and before taking effect. However, ticagrelor, which belongs to the cyclopentyl-triazolol-pyrimidine family, directly reversibly inhibits the P2Y₁₂-ADP receptor. Thus, the theoretical onset time is shorter than that of clopidogrel.³⁰ In the ONSET/OFFSET study, patients with stable coronary disease were selected as research objects and were randomly assigned to receive treatment with loading dose ticagrelor (180 mg, $n=57$) or clopidogrel (600 mg, $n=54$).³¹ The mean time to maximal platelet inhibition was ~2 hours in the ticagrelor group and 7.8 hours in the clopidogrel group. In particular, platelet inhibition was higher in the ticagrelor group at 0.5 hour (41% vs 8%, $P<0.0001$), indicating that the onset time of ticagrelor was very short. Another study used a VerifyNow device to detect changes in P2Y₁₂ reaction units (PRUs) after loading dose ticagrelor and clopidogrel in patients with ACS undergoing PCI who were low-risk, troponin-negative, and had not used P2Y₁₂ receptor inhibitor previously.³² After 2 hours of loading dose, the PRU of the ticagrelor group was significantly lower than that of the clopidogrel group (98.4 vs 257.5, $P<0.001$). This experimental design ruled out the impact of previous use of P2Y₁₂ receptor antagonist

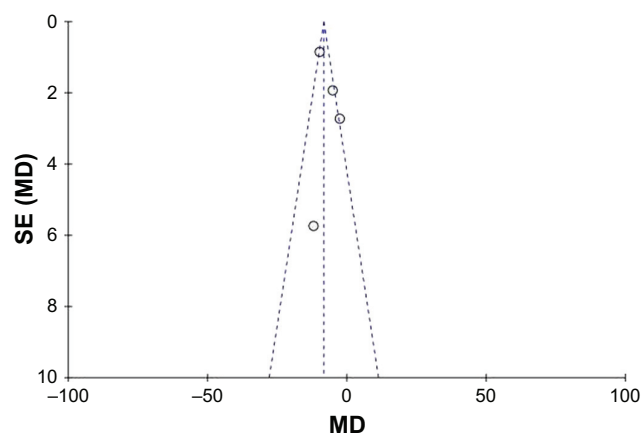


Figure 5 Funnel plot of the change of cTFC after PPCI.

Abbreviations: cTFC, corrected TIMI frame count; TIMI, thrombolysis in myocardial infarction; PPCI, primary percutaneous coronary intervention; MD, mean difference.

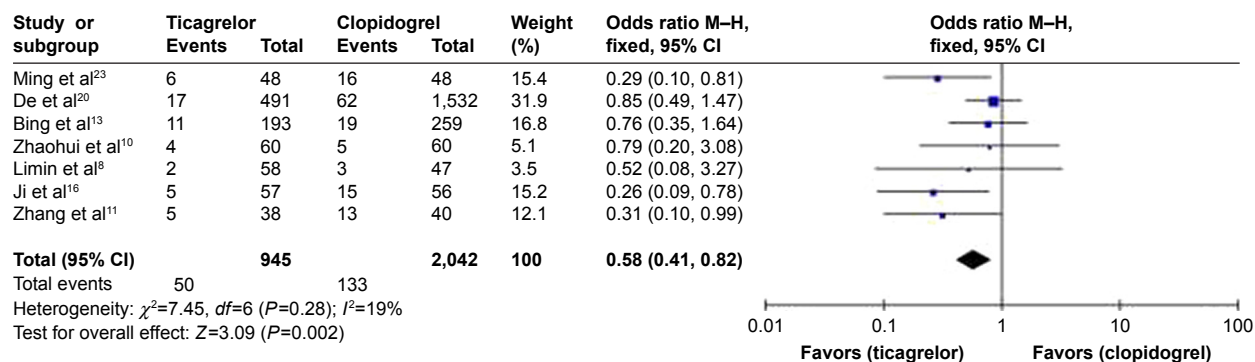


Figure 6 Forest plot of MACE in hospital or within 30 days after PPCI.

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; PPCI, primary percutaneous coronary intervention.

and probably reflected the rapid effect of antiplatelet of ticagrelor.

Despite the potent and fast platelet inhibition of the P2Y₁₂ receptor inhibitor ticagrelor, other effects associated with NRF were also found. Adenosine, as a common metabolite, increases coronary flow velocity and inhibits platelet activation by the A_{2A} and A_{2B} receptors.³³ However, adenosine is usually taken up rapidly by erythrocytes in vivo and thus cannot maintain the effect of inhibiting platelets for a long time.³⁴ Bonello et al designed a study in which 60 patients with ACS were randomized to a ticagrelor group or a clopidogrel group, and the results showed that the patients in the ticagrelor group had higher plasma levels of adenosine, suggesting that ticagrelor increased the plasma concentration of adenosine.³⁵ The mechanisms explaining this result could be that ticagrelor not only promoted the ATP that came from the degradation of erythrocytes into adenosine³⁶ but also inhibited the ENT1 pathway on the erythrocyte membranes to reduce the uptake of adenosine by erythrocytes.³⁷ This effect of higher levels of adenosine provides ticagrelor with an additional antiplatelet function that other P2Y₁₂ receptor inhibitors do not have. Moreover, the adenosine-mediated antiplatelet pathway enhanced the antiplatelet effect of

ticagrelor and possibly reduced the formation of microembolization that was associated with the mechanical occlusion of microvessels, resulting in the NRF phenomenon and the activation of the coagulation and inflammation pathways.^{7,38} In addition, other studies have shown that adenosine acted on vascular endothelium A_{2A} receptor to dilate coronary arteries,³⁹ increase coronary blood flow,³³ reduce myocardial infarct size,⁴⁰ and reduce ischemia and reperfusion injury.⁴¹ Therefore, adenosine can play a role in protecting the heart. In another study,⁴² by using adenosine receptor antagonists, the myocardial protective effect of ticagrelor was reversed. Thus, it demonstrated that this protective effect was mediated by increasing adenosine not by P2Y₁₂ receptor antagonism.

By contrast, the results of our meta-analysis showed that preoperative loading dose ticagrelor significantly increased the number of patients whose coronary blood flow of IRA restored TIMI3 after PPCI ($P<0.05$), suggesting that the ticagrelor group had better IRA reperfusion after PPCI. In addition, the level of cTFC was more precise than TIMI blood flow for evaluating the reperfusion of coronary blood flow. As we know, the lower the cTFC level is, the faster the blood flow reaches the distal portion of the coronary vessel. In our study, the level of cTFC in the preoperative loading

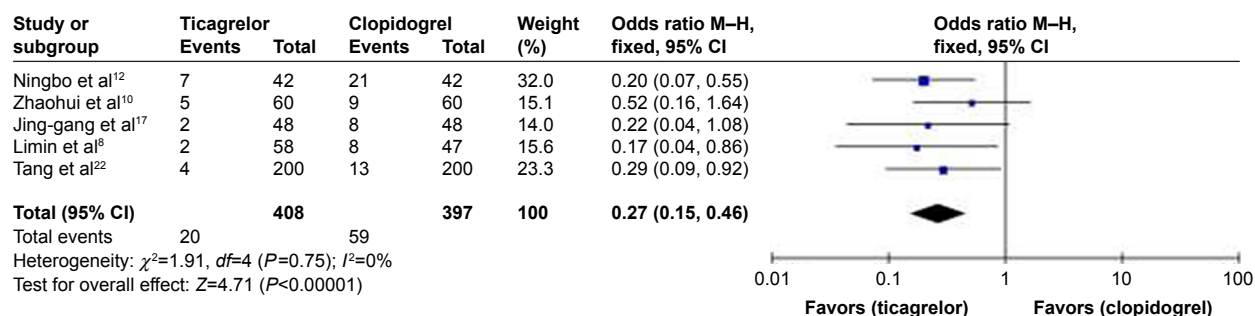


Figure 7 Forest plot of MACE within 180 days after PPCI.

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; PPCI, primary percutaneous coronary intervention.

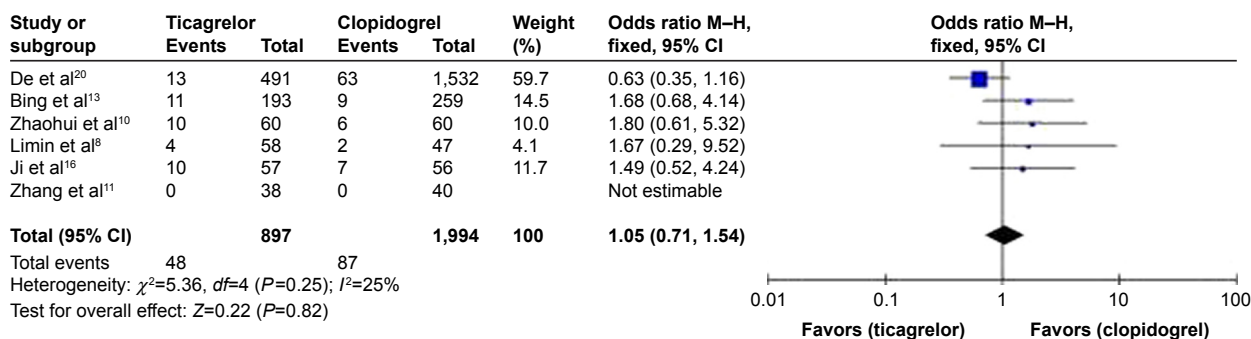


Figure 8 Forest plot of bleeding events within 30 days after PPCI. **Abbreviations:** CI, confidence interval; PPCI, primary percutaneous coronary intervention.

dose ticagrelor group after PPCI was significantly lower than that of the clopidogrel group ($\chi^2=9.75, I^2=69\%, 95\% \text{ CI}: -9.89, -6.91, P<0.05$). Although the I^2 test was $>50\%$, according to the funnel plot (Figure 5) of the cTFC levels, we found that all four articles were in the funnel, suggesting that the heterogeneity remained in acceptable range. Simultaneously, we found that preoperative loading dose ticagrelor significantly reduced the number of patients who suffered MACE during hospitalization or within 30 days after PPCI (95% CI: 0.41, 0.82, $P<0.05$) and within 180 days after PPCI (95% CI: 0.15, 0.46, $P<0.05$) without an increased number of bleeding events within 30 days after PPCI (95% CI: 0.71, 1.54, $P=0.82$) and within 180 days after PPCI (95% CI: 0.81, 3.19, $P=0.18$). This result suggested that in the ticagrelor group, patients with STEMI after PPCI obtained more clinical benefits without a higher risk of bleeding compared with the clopidogrel group. This consequence was consistent with the results of the PPCI subgroup in the PLATO trial,⁴ including 7,544 patients with STEMI.

There are several limitations of our meta-analysis. First, the subjects in most of the included studies were Chinese. Thus, the conclusions obtained from this meta-analysis may be suitable only for Chinese populations. These findings might change in studies of various races and nationalities. In addition, the *CYP2C19* gene polymorphism, which has an

influence on the effect of clopidogrel, was not considered. However, the incidence of carriers with *CYP2C19**2 and *3 alleles, which leads to the lower reaction of clopidogrel, in the Asian population was higher than that of the European and African populations,⁴³⁻⁴⁵ suggesting that the antiplatelet effect of clopidogrel was underestimated if the included patients had alleles leading to low response to clopidogrel in Asia. Second, some of the studies included in our meta-analysis had their own limitations, especially in describing the randomization method, allocation method, and inclusion criteria. In addition, our study included an observational study that is weaker than RCTs in terms of strength of evidence. Third, only four articles described the onset of chest pain to opening of the IRA, and three articles described the time to loading and PCI. It is generally believed that the duration of ischemia is positively correlated with the degree of myocardial necrosis, resulting in different prognoses. Nevertheless, there was no difference between the groups in the reported studies. However, it was unclear whether the time to loading and PCI in other studies made a difference that would cause heterogeneity or produce effects on the final analysis. Finally, most of the studies included in our meta-analysis were published in Chinese journals, so the quality of the articles may not be as high as the quality of those published in English-language journals.

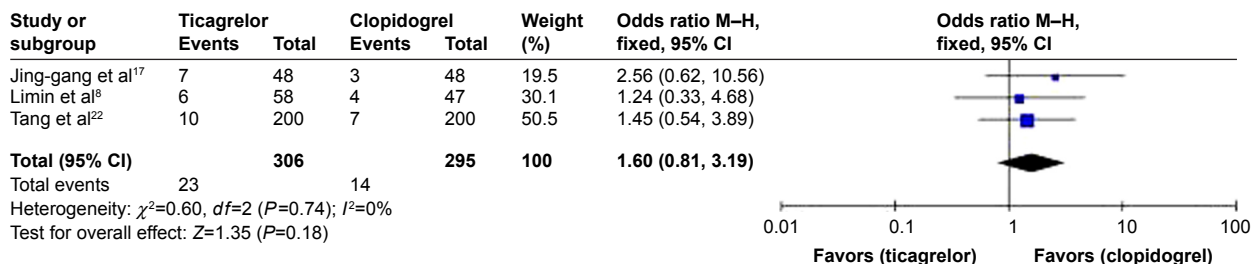


Figure 9 Forest plot of bleeding events within 180 days after PPCI. **Abbreviations:** CI, confidence interval; PPCI, primary percutaneous coronary intervention.

Conclusion

Our meta-analysis suggests that compared with clopidogrel, treatment with preoperative loading dose ticagrelor in patients with STEMI effectively reduces the occurrence of the NRF phenomenon during PPCI and near-term MACE. At the same time, loading dose ticagrelor does not increase the risk of bleeding, either in the hospital or within 180 days after PPCI. Due to the limitations in the quantity and quality of studies included in this article, these conclusions need to be confirmed by more high-quality multicenter clinical trials.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Sasko K, Oliver K, Slobodan A, Jorgo K, Hristo P, Igor S. The prevalence and outcomes of transradial percutaneous coronary intervention for acute coronary syndrome. Analysis from the single-centre ISACS-TC Registry (International Survey of Acute Coronary Syndrome in Transitional Countries) (2010–12). *Eur Heart J Suppl.* 2014; 16(Suppl_A):A33–A41.
- Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2010;56(18):1456–1462.
- Giorgi MA, Cohen AH, Gonzalez CD, Di Girolamo G. Beyond efficacy: pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. *Expert Opin Pharmacother.* 2011;12(8):1285–1295.
- Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation.* 2010;122(21):2131–2141.
- Wozakowskakaplon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. *Cardiol J.* 2009;16(5):462–468.
- Kopetz VA, Penno MAS, Hoffmann P, Wilson DP, Beltrame JF. Potential mechanisms of the acute coronary syndrome presentation in patients with the coronary slow flow phenomenon – insight from a plasma proteomic approach. *Int J Cardiol.* 2012;156(1):84–91.
- Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J Am Coll Cardiol.* 2009;54(4):281–292.
- Liming X, Xiaoming W, Rui Y, et al. Effect and safety of pre-operative loading ticagrelor on myocardium reperfusion in patients with acute ST-elevation myocardial infarction during primary percutaneous coronary intervention. *Chin Circ J.* 2016;31(6):550–554.
- Montalescot G, Lassen JF, Hamm CW, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: Rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath lab or in the Ambulance for New ST elevation myocardial infarction to open the Coronary artery (ATLANTIC) study. *Am Heart J.* 2013;165(4):515–522.
- Chaohui W, Haimiao L, Zhiyuan H, et al. Effect and safety of ticagrelor on patients with acute myocardial infarction undergoing primary percutaneous intervention with no-reflow. *J Clin Cardiol (China).* 2015;(7):708–712.
- Zhang DW, Kang YX, Liu LY, et al. Impact of ticagrelor on coronary slow flow during emergency PCI in patients with acute ST segment elevation myocardial infarction. *Chin Pract J Card Cereb Pneumal Vasc Dis.* 2015;23(9):7–10.
- Ningbo L, Dongmei W, Anjia S, et al. Effect of ticagrelor on coronary blood flow in patients with acute ST-segment elevation myocardial infarction and reperfusion. *J Third Mil Med Univ.* 2016;38(17):1976–1981.
- Bing Q, Shaoping N, Chunmei W, et al. Protection of ticagrelor on myocardium in patients with ST-segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. *J Clin Cardiol (China).* 2015;(11):1171–1174.
- Yujun Z. Myocardium-protective effects of ticagrelor combined with emergency PCI treatment of acute myocardial infarction and the possible molecular mechanisms. *J Hainan Med Univ.* 2016;22(17):1940–1942.
- Fangcheng S, Fang Z. Clinical efficacy and safety of ticagrelor with primary PCI for acute myocardial infarction in the perioperative period. *J Clin Cardiol (China).* 2015;(1):27–30.
- Ji X, Qi H, Shaodong H, et al. Efficacy and safety of ticagrelor combined with primary PCI in elderly patients with ST-elevated acute myocardial infarction. *J Cap Med Univ.* 2015;36(1):73–77.
- Jing-gang X, Yang Q, Shaodong H, et al. Midterm follow up outcomes of ticagrelor on acute ST segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. *J Peking Univ.* 2015; 47(3):494–498.
- Mont'Alverne-Filho JR, Rodrigues-Sobrinho CRM, Medeiros F, et al. Upstream clopidogrel, prasugrel, or ticagrelor for patients treated with primary angioplasty: results of an angiographic randomized pilot study. *Catheter Cardiovasc Interv.* 2016;87(7):1187–1193.
- Zhu K, Fu Q, Zhang N, Huang YJ, Zhang Q. Pre-PCI medication using clopidogrel and ticagrelor in the treatment of patients with acute myocardial infarction. *Eur Rev Med Pharmacol Sci.* 2015;19(23): 4636–4641.
- De BO, Ratcovich H, Biasco L, et al. Prehospital administration of P2Y12 inhibitors and early coronary reperfusion in primary PCI: an observational comparative study. *Thromb Haemost.* 2015;114(3):623–631.
- Winter JL, Lindefeld DS, Veas N, et al. Angiographic and electrocardiographic parameters of myocardial reperfusion in angioplasty of patients with ST elevation acute myocardial infarction loaded with ticagrelor or clopidogrel (MICAMI – TICLO trial). *Cardiovasc Revasc Med.* 2014; 15(5):284–288.
- Tang X, Li R, Jing Q, et al. Assessment of ticagrelor versus clopidogrel treatment in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Cardiovasc Pharmacol.* 2016;68(2):115–120.
- Ming L, Yun-feng D, Xing C. Efficacy of tigraverol combined with emergency PCI in the treatment of acute ST-segment elevation myocardial infarction in diabetic patients. *N World Diabet.* 2016;19(11):36–37.
- Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2016;133(11):1237–1250.
- Feng T, Dai CY. Studies on the study of coronary artery reflow phenomenon. *Chin J Circ.* 2004;19:472–475.
- Brosh D, Assali AR, Mager A, et al. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. *Am J Cardiol.* 2007;99(4):442–445.

27. Ndrepepa G, Tiroch K, Keta D, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. *Circulation*. 2010;3(1):27–33.
28. Niccoli G, Scalone G, Lerman A, et al. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J*. 2016;37(13):1024–1033.
29. Gupta S, Gupta MM. No reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction. *Indian Heart J*. 2016;68(4):539–551.
30. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol*. 2015;12(1):30–47.
31. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease. *Circulation*. 2009;120(25):2577–2585.
32. Angiolillo DJ, Franchi F, Waksman R, et al. Effects of ticagrelor versus clopidogrel in troponin-negative patients with low-risk ACS undergoing ad hoc PCI. *J Am Coll Cardiol*. 2016;67(6):603–613.
33. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. *J Am Coll Cardiol*. 2013;61(7):723–727.
34. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014;63(23):2503–2509.
35. Bonello L, Laine M, Kipson N, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. *J Am Coll Cardiol*. 2014;63(9):872–877.
36. Ohman J, Kudira R, Albinsson S, et al. Ticagrelor induces adenosine triphosphate release from human red blood cells. *Biochem Biophys Res Commun*. 2012;418(4):754–758.
37. Nylander S, Femia EA, Scavone M, et al. Ticagrelor inhibits human platelet aggregation via adenosine in addition to P2Y12 antagonism. *J Thromb Haemost*. 2013;11(10):1867–1876.
38. Bonderman D, Teml A, Jakowitsch J, et al. Coronary no-reflow is caused by shedding of active tissue factor from dissected atherosclerotic plaque. *Blood*. 2002;99(8):2794–2800.
39. Mustafa SJ, Morrison RR, Teng B, et al. Adenosine receptors and the heart: role in regulation of coronary blood flow and cardiac electrophysiology. *Handb Exp Pharmacol*. 2009;193(193):161–188.
40. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Bimbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size. *Arterioscl Thromb Vasc Biol*. 2014;34(9):2078–2085.
41. Headrick JP, Lasley RD. Adenosine receptors and reperfusion injury of the heart. *Handb Exp Pharmacol*. 2009;(193):189–214.
42. Torngren K, Öhman J, Salmi H, Larsson J, Erlinge D. Ticagrelor improves peripheral arterial function in patients with a previous acute coronary syndrome. *Cardiology*. 2013;124(4):252–258.
43. Xie HG, Stein CM, Kim RB, et al. Allelic, genotypic and phenotypic distributions of S-mephenytoin 4'-hydroxylase (CYP2C19) in healthy Caucasian populations of European descent throughout the world. *Pharmacogenetics*. 1999;9(5):539–549.
44. Xie HG, Kim RB, Stein CM, Wilkinson GR, Wood AJ. Genetic polymorphism of (S)-mephenytoin 4-hydroxylation in populations of African descent. *Br J Clin Pharmacol*. 1999;48(3):402–408.
45. Ailing Z, Liping Y, Xin H. Allele frequencies of CYP2C19 gene in healthy Asian populations: a synthetic analysis. *Chin J Evid Based Med*. 2013;13(12):1431–1439.

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