Am J Transl Res 2018;10(7):2175-2183
www.ajtr.org /ISSN:1943-8141/AJTR0076812

Original Article

Clinical efficacy of ticagrelor in patients undergoing emergency intervention for acute myocardial infarction and its impact on platelet aggregation rate

Hai-Bo Wu, Huan-Ping Tian, Xue-Chao Wang, Shi-Ru Bai, Xin-Ning Li, Li-Na Zhang, Rong-Pin Du

Department of Cardiology, Hebei General Hospital, Shijiazhuang 050000, Hebei, China

Received March 27, 2018; Accepted June 9, 2018; Epub July 15, 2018; Published July 30, 2018

Abstract: Objective: This study aims to investigate the clinical efficacy of ticagrelor in patients who underwent emergency percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI), and its impact on platelet aggregation rate. Methods: A total of 257 AMI patients who underwent emergency PCI in our hospital were included in the present study. These patients were randomly divided into two groups: ticagrelor group (n = 129), patients took 180 mg of ticagrelor (*qd*) before the intervention, and subsequently took 90 mg of ticagrelor (*bid*) for maintenance; clopidogrel group (n = 128), patients took 300 mg of clopidogrel (*qd*) before PCI, and subsequently took 75 mg of clopidogrel (*qd*) for maintenance. Patients in both groups took 100 mg of aspirin. The major adverse cardiovascular events (MACE) within one year, changes in LVEF and LVEDD, platelet aggregation rate and drug safety before PCI and at one week and 30 days after PCI were observed in these two groups. Results: The differences in baseline data between these two groups were not statistically significant. Within one year after the intervention, in the ticagrelor group, the total incidence of MACE was lower ($P < 0.05$), LVEF and LVEDD was improved ($P < 0.05$), and the decrease in platelet aggregation rate after the intervention was more significant ($P < 0.05$). Furthermore, the incidence of bleeding events was higher in the ticagrelor group than in the clopidogrel group ($P < 0.05$). Conclusions: Compared with clopidogrel, ticagrelor decreases the incidence of adverse cardiovascular events in AMI patients who underwent emergency PCI, does better in improving the fluctuation level of LVEF and LVEDD, and strongly inhibits platelet aggregation. Some patients encountered adverse drug events, but drug withdrawal or medication change did not occur.

Keywords: Ticagrelor, acute myocardial infarction, emergency intervention, platelet aggregation rate

Introduction

The prevalence of cardiovascular disease in China has an increasing trend. In 2015, among the causes of disease-related deaths in urban and rural residents, vascular disease ranked at the top [1]. Acute myocardial infarction (AMI) is the first cause of death due to cardiovascular disease [2]. Direct percutaneous coronary intervention (PCI) is the first choice of reperfusion therapy for AMI patients within 12 hours after onset. *Lancet* suggests that direct PCI is the most effective treatment to reduce the mortality of patients with ST-segment elevation myocardial infarction (STEMI). Since thrombi easily form during the operation, antiplatelet therapy is the key [3] for the prevention and treatment of thrombosis. Aspirin combined with clopidogrel is a conventional dual-drug therapy. However, the efficacy of clopidogrel varies from person to person. In some patients, it does not reach the desired results, or even induces myocardial infarction, stroke and thrombotic events [4]. Ticagrelor is a novel reversible P2Y12 receptor antagonist, which can more rapidly and strongly inhibit platelet aggregation. Furthermore, it further improves the prognosis of patients with acute coronary syndromes (ACS), when compared with clopidogrel [5-7]. Moreover, ticagrelor increases plasma adenosine concentration [8], improves myocardial perfusion and microcirculation [9], and further improves heart function. The application of ticagrelor has gradually become extensive, but the understanding of its clinical application remains poor. The aim of the present

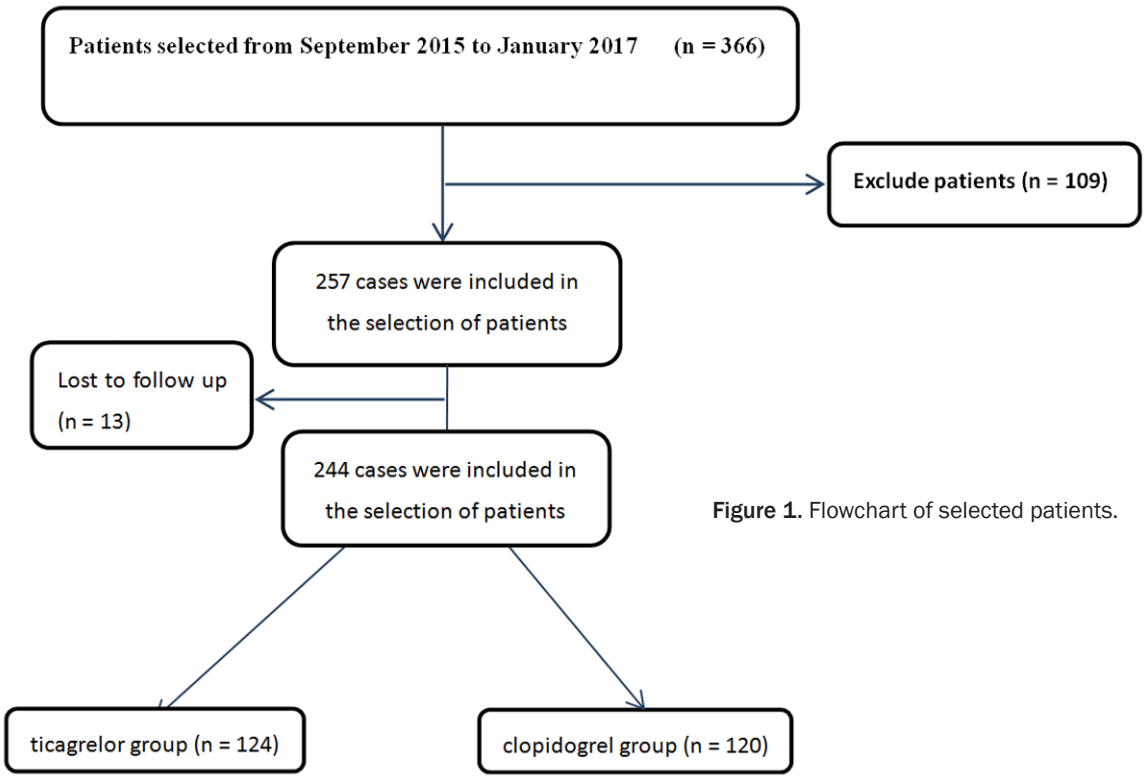

Figure 1. Flowchart of selected patients.

study was to assess the efficacy and safety of ticagrelor in patients who underwent emergency intervention for AMI, and investigate its impact on left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD) and platelet aggregation rate.

Subjects and methods

Subjects

A total of 257 AMI patients who were treated with emergency PCI in the Emergency Department of Hebei General Hospital from September 2015 to January 2017 were consecutively included in the present study. These patients were randomly divided into two groups: ticagrelor group (n = 129) and clopidogrel group (n = 128). Patients in both groups all orally took a loading dose of aspirin (300 mg). After diagnosis, patients in the clopidogrel group took 300 mg of clopidogrel (*qd*), and subsequently took 75 mg of clopidogrel (*qd*) for maintenance. Patients in the ticagrelor group took 180 mg of ticagrelor (*qd*), and subsequently took 90 mg of ticagrelor (*bid*) for maintenance. All patients met the Guidelines for the Diagnosis and Treatment of Acute ST-segment Elevation Myocardial Infarction 2015, and met the diagnostic criteria in the Diagnosis and Treatment Guidelines for Non ST-segment Elevation Acute Coronary Syndromes 2016. The exclusion criteria are as follows. This study was approved by the Ethics Committee of our hospital, and met the ethical requirements.

Research methods

Inclusion criteria: (1) Non STEMI patients should meet at least two of the following criteria; (1) the electrocardiogram (ECG) presented with decreased ST segments in ≥ 2 consecutive leads or ≥ 0.1 mv of transient elevated ST segment; (2) assay results of the myocardial injury markers (such as Mb or CK-MB, or cTnI or cTnT) were positive; (3) patients presented with at least one of the following risk factors: age ≥ 60 years old, hyperlipidemia, hypertension, diabetes mellitus, history of myocardial infarction, ≥ 50% vascular stenoses in ≥ 2 branches of the coronary artery, history of cerebral infarction, transient ischemic attack (TIA) diagnosed by the hospital, carotid canal presented with ≥ 50% stenosis, history of revascularization of cerebral blood vessels, peripheral arterial disease, and chronic renal dysfunction. (2) STEMI

Table 1. Comparison of clinical data of two groups of patients

Item	Ticagrelor group (n = 124)	Clopidogrel group (n = 120)	P
Male (case %)	98 (79.0)	94 (78.3)	0.894
Age (year)	58.976 ± 10.187	61.058 ± 11.600	0.137
Acute non ST segment elevation myocardial infarction (case %)	7 (5.6)	5 (4.2)	0.593
History of smoking (case %)	78 (62.9)	73 (60.8)	0.739
History of hypertension (case %)	64 (51.6)	69 (57.5)	0.356
Diabetes (case %)	32 (25.8)	25 (20.8)	0.359
Dyslipidemia (case %)	15 (12.1)	15 (12.5)	0.924
KillipI-II grade of heart failure (case %)	122 (98.4)	114 (95.0)	0.260
EDD (mm)	48.065 ± 4.592	48.474 ± 4.639	0.490
LVEF (%)	56.075 ± 7.851	55.846 ± 9.195	0.8343
BNP (pg/ml)	877.028 ± 778.882	864.289 ± 713.365	0.930
Creatinine (umol/l)	84.737 ± 17.084	85.725 ± 16.174	0.727
Nitrates	41 (33.1)	38 (31.7)	0.816
ARB/ACEI	83 (66.9)	78 (65.0)	0.750
β-blockers	109 (87.9)	101 (84.2)	0.399
Calcium antagonist	3 (2.4)	4 (3.3)	0.965
Statins	116 (93.5)	114 (95.0)	0.626
Proton pump inhibitor	61 (49.2)	57 (47.5)	0.791
Preoperative TIMI blood flow			
Grade 0 of blood flow	95 (77.6)	80 (66.7)	0.085
Grade 1-2 of blood flow	14 (11.3)	21 (17.5)	0.167
Grade 3 of blood flow	15 (12.1)	19 (15.8)	0.399
Postoperative TIMI blood flow			
Grade 3 of blood flow	122 (98.4)	119 (99.2)	1.00

patients should meet the following criteria: the ECG presented with elevated ST segments in ≥ 2 consecutive leads and ≥ 0.1 mv, or a left bundle branch block was newly detected.

*Exclusion criteria: (**Figure 1**)*: 1. Patients had severe heart failure (NYHA III-IV). 2. Patients had contraindications to aspirin, clopidogrel, or ticagrelor, or patients had intolerance due to other causes, such as active bleeding, moderate/severe liver disease, severe kidney disease, or patients changed the drug in midway. 3. Patients had coagulation disorders, or a history of intracranial hemorrhage, or a history of hemorrhage in the digestive tract in the past six months, or a history of major surgery in the past 30 days. 4. Patients had chronic obstructive pulmonary disease, or bronchial asthma.

Administration method: The present study is a randomized controlled study. After the patients were diagnosed, and before PCI patients in the experimental group were given ticagrelor (Brilinta, AstraZeneca), the loading dose at the first day was 180 mg/times (*qd*), and the subsequent dose was 90 mg/times (*bid*). Patients in the clopidogrel group orally took clopidogrel bisulfate tablets (Talcom tablets, Shenzhen Salubris Pharmaceuticals Co. Ltd.), the loading dose at the first day was 300 mg/times (*qd*), and the subsequent dose was 75 mg/times (*qd*). Patients in both groups took aspirin (Bayaspirin Enteric-coated Tablets, Bayer Health Care), the loading dose at the first day was 300 mg/times (*qd*), and the subsequent dose was 100 mg/times (*qd*). Patients with contraindications were excluded, and the included patients were given statins and β-receptor blockers.

Laboratory assay

The levels of platelet aggregation in the two groups of patients were detected and recorded before intervention, and at one week and 30 days after the intervention.

Table 2. Comparison of the major adverse cardiovascular events in the two groups [case (%)]

Item (case %)	Ticagrelor group (n = 124)	Clopidogrel group (n = 120)	P
Recurrent angina pectoris	4 (3.2)	13 (10.8)	0.020
Recurrent myocardial infarction	0	3 (2.5)	0.234
Stroke	1 (0.8)	4 (3.3)	0.347
Heart failure	3 (2.4)	5 (4.2)	0.684
Stent thrombosis	0	0	
Other thrombus events	1 (0.80)	3 (2.50)	0.591
Cardiovascular death	0	2 (1.7)	0.463
Total incidence	9 (7.3)	30 (25)	0.000

Note: P < 0.05 has statistical significance.

Detection methods: In these two groups, before emergency PCI, and at one week and 30 days after PCI, venous blood was withdrawn from patients and centrifuged. Then, with 5 μmol/L of ADP as an inducer, platelet aggregation rate was measured using the AggRAM platelet aggregation analysis system (Helena, USA).

Clinical data acquisition

The clinical data of patients in these two groups were collected and recorded by consulting electronic medical records and physical examination data, which included the gender, age, smoking history, hypertension, diabetes, dyslipidemia, LVEF, LVEDD, brain natriuretic peptide (BNP), creatinine, clinical medication and blood flow classification data before and after PCI.

Follow-up method and observation index

One year after PCI, the two groups of patients were followed-up by accessing their electronic medical records and through telephone follow-up. The patients' MACEs (including recurrent angina, recurrent myocardial infarction, stroke, heart failure, in-stent thrombosis, other thromboembolic events and cardiovascular death) during the medication period were recorded, LVEF, LVEDD and drug-related adverse reactions (including bleeding, dyspnea and bradycardia) were checked at one year after PCI, and the platelet and ADP aggregation rates were determined at one week and 30 days after PCI.

Statistical analysis

Data were analyzed using statistical software SPSS 21.0. Normally distributed measurement data were presented as mean ± standard deviation (x ± SD), and compared using independent sample *t*-test. Measurement data in non-normal distribution were presented as the median, and compared using independent sample nonparametric *U*-test. Count data were compared using the X^2-test. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical data

Differences in baseline data, AMI type and drug use between these two groups were not statistically significant (**Table 1**).

Comparison of MACE: These two groups of patients were followed up for one year. Five subjects were lost to follow-up in the ticagrelor group, while eight subjects were lost to follow-up in the clopidogrel group. Within one year after PCI, in the ticagrelor group, four patients had recurrent angina pectoris, no patient had myocardial infarction, one patient had stroke, three patients had heart failure, one patient had other thrombus and no cardiovascular deaths occurred. In the clopidogrel group, thirteen patients had recurrent angina pectoris, three patients had myocardial infarction, four patients had stroke, five patients had heart failure, three patients had other thrombus and two cardiovascular deaths occurred. In both groups, no patient had in-stent thrombosis. The incidence of recurrent angina pectoris was lower in the ticagrelor group than in the clopidogrel group, and the difference was statistically significant ($P < 0.05$, **Table 2**).

Comparison of changes in LVEF and LVEDD between the two groups before and at one year after the intervention

At one year after the intervention, the level of LVEF was higher in the ticagrelor group than in the clopidogrel group. In both groups, the levels of LVEF were higher at one year after the intervention, compared to levels before the intervention, and the differences before and after the intervention were statistically significant (*P*

Table 3. Comparison of the changes of the two groups of LVEF and LVEDD

Group	LVEF (%)			LVEDD (mm)		
	Preoperative	1 years after the operation	P	Preoperative	1 years after the operation	P
Ticagrelor group	56.075 ± 7.851	59.3011 ± 8.145	0.000	48.065 ± 4.592	47.194 ± 3.187	0.016
Clopidogrel group	55.846 ± 9.195	56.846 ± 10.684	0.379	48.474 ± 4.639	49.513 ± 5.014	0.063

Table 4. Determination of platelet aggregation rate of antiplatelet ADP in two groups

Item	Ticagrelor group ($\bar{\chi}$ ± s)	Clopidogrel group ($\bar{\chi}$ ± s)	P
Preoperative	73.909 ± 12.381	76.573 ± 12.145	0.704
1 weeks after operation	40.410 ± 18.024	45.7308 ± 14.742	0.386
30 days after operation	29.368 ± 15.263	46.342 ± 21.956	0.003

Table 5. Comparison of the safety of the two groups of drugs [case (%)]

Item	Ticagrelor group (case)	Clopidogrel group (case)	P
Hemorrhagic event	14 (11.0)	4 (3.3)	0.020
Dyspnea	3 (2.4)	0	0.257
Bradycardia	1 (0.8)	0	1.000
Total incidence	18 (14.5)	4 (3.3)	0.002

< 0.05). The difference in the level of LVEDD before and after intervention in the ticagrelor group was statistically significant ($P < 0.05$). However, the difference in the level of LVEDD before and after intervention in the clopidogrel group was not statistically significant (**Table 3**).

Comparison of platelet aggregation rates between the two groups

The platelet aggregation rates at one week and 30 days after the intervention in the ticagrelor and clopidogrel groups were lower than those before the intervention, the decrease was more obvious in the ticagrelor group than in the clopidogrel group, and the inhibition effect remained strong in the ticagrelor group after 30 days ($P < 0.05$). Its strong effect of anti platelet aggregation could be maintained when the medication was continued (**Table 4**).

Comparison of drug safety between the two groups

In these two groups, no massive hemorrhage event occurred, and bleeding events manifested as minor bleeding events such as gingival bleeding and epistaxis. The incidence of minor bleeding events was higher in the ticagrelor group than in the clopidogrel group, and the difference was statistically significant. These minor bleeding events could be stopped when the corresponding treatment was given, and no drug withdrawal caused by minor bleeding occurred. The total incidence of adverse events after drug use was higher in the ticagrelor group than in the clopidogrel group, and the difference between these two groups was statistically significant. However, no drug withdrawal caused by adverse events occurred (**Table 5**).

Discussion

The standardized treatment of AMI, the shortening of occlusion time in infarct-related artery (IRA), early diagnosis and early reperfusion therapy have become the key links of AMI treatment. Furthermore, emergency PCI can be more effective in recanalizing blood vessels, which improves the success rate of rescue of AMI patients, reduces the mortality, and benefits the majority of patients [2]. A recent study has emphasized that after STEMI patients were treated with reperfusion therapy, PCI, modern antithrombotic therapy and secondary prevention, the rates of acute and long-term mortality decreased [10]. Furthermore, the application of aspirin and P2Y12 receptor inhibitors achieves sufficient platelet inhibition, and ensures the safe and effective operation of PCI. Antiplatelet drug therapy is the basis for the management of patients with myocardial infarction. Aspirin combined with clopidogrel is used as a conventional dual antiplatelet drug therapy (DAPT). For

patients receiving thrombolytic therapy and subsequent PCI treatment, it is recommended to provide DAPT for 12 months. Clopidogrel has been used as a P2Y12 inhibitor in combination treatments and post-fibrinolysis treatments [11]. Two studies have revealed that in patients treated with DAPT for more than 12 months, the incidence of non-fatal ischemic events was reduced [12, 13]. Clopidogrel, which is an irreversible P2Y12 inhibitor, has been widely used in coronary artery disease, including AMI. However, people remain concerned about its genetic susceptibility and delayed antiplatelet effect [14]. In the clopidogrel metabolic pathway, the *CYP2C19* gene is of great significance [15]. The dysfunctional CYP2C19 allele may cause a decrease in the production of effective metabolites of clopidogrel, which impairs the antiplatelet effect and increases the risk of recurrent ischemic events [16]. A study revealed that 5-40% of patients had a partial response or no response to clopidogrel, which was defined as "clopidogrel resistance" [17]. Directing at the resistance to clopidogrel, guidelines have pointed out that the first choice is to increase the dose of clopidogrel. The results of the CURRENT OASIS 7 trials revealed that a double dose of clopidogrel could significantly reduce the incidence of major endpoint events, compared with a standard dose. In addition, it could significantly reduce in-stent thrombosis. However, another study revealed that the benefit of increasing the dose was not obvious. Therefore, merely doubling the maintenance dose of clopidogrel may be not enough. The second choice is to replace clopidogrel by other antiplatelet drugs, such as ticagrelor and prasugrel. The overall efficacy of both was superior to clopidogrel [18]. The genetic subgroup analysis in the Platelet Inhibition and Patient Outcomes (PLATO) trial revealed that regardless of whether the patient carried the CYP2C19 allele with function deletion, the curative effect of ticagrelor was better than that of clopidogrel in treating ACS [19]. This promotes the application of ticagrelor, which is a CYP2Y12 receptor antagonist.

Ticagrelor is a member of the chemical taxonomy of cyclopentyl-triazole-pyrimidine (CPTP), which is an adenosine diphosphate (ADP) receptor antagonist. It selectively binds with the P2Y12ADP receptor [20-22]. Although ticagrelor has a mechanism similar to clopidogrel, ticagrelor exhibits a significant advantage of reversible binding with the P2Y12 ADP receptor. Therefore, once the effect of the drug terminates, the platelet reaction can be recovered, and platelet function is not affected. Hence, the long-term use of ticagrelor does not increase the risk of thrombosis [23]. In addition, ticagrelor can directly work without activation by liver metabolism, and rapidly produce its main circulating metabolite AR-C124910XX. Itself and its metabolite can reversibly bind with the platelet P2Y12ADP receptor and take the role.

The PLATO trial pointed out that in ACS patients, the application of ticagrelor significantly decreased the mortality of cardiovascular disease, myocardial infarction, or stroke, when compared with clopidogrel. Without significantly increasing the bleeding rate, ticagrelor fully plays a beneficial role. In ACS patients with or without STEMI, it could be observed that the benefits of ticagrelor were superior to clopidogrel [7]. In a double-blinded, multicenter, event-driven clinical trial [7], 18,624 ACS patients were enrolled and randomly divided into two groups: ticagrelor group and clopidogrel group. Patients in the ticagrelor group received a loading dose of 180 mg of ticagrelor, and subsequently received 90 mg (*bid*) of ticagrelor for maintenance. Patients in the clopidogrel group received a loading dose of 300-600 mg of clopidogrel, and subsequently received 75 mg (*qd*) of clopidogrel for maintenance. After 12 months of follow-up, with cardiovascular death, myocardial infarction and stroke as the main endpoint events, the incidence was significantly lower in the ticagrelor group than in the clopidogrel group ($P < 0.001$). Varenhorst *et al*. revealed that [24] ticagrelor could not only inhibit platelets, but also prevent vascular endothelium and cardiomyocyte damage caused by platelet aggregation, playing an indirect role in the repair of blood vessels and the protection of the myocardium. Since the precondition for myocardial survival is good myocardial perfusion, the increase in the number of surviving myocardial cells inhibits the left ventricular reconfiguration and influences the function of the whole heart. Therefore, at 24 hours after the operation, in the ticagrelor group, the level of LVEF significantly increased and the level of LVEDD significantly decreased. These results verified again that good myocardial perfusion

and the recovery of normal blood flow after the use of ticagrelor inhibit left ventricular reconfiguration after infarction to a certain extent, accordingly improve the prognosis of patients [25], and has an indirect protective effect in improving the systolic and diastolic function of the heart, thereby improving long-term cardiac function. In the present study, after one year of follow-up, it was found that the incidence of adverse cardiovascular events was lower in the ticagrelor group than in the clopidogrel group. For anti platelet aggregation, the inhibitory effect on platelet aggregation was more obvious in the ticagrelor group than in the clopidogrel group, and its benefit of inhibiting platelet aggregation can be continuously maintained during the drug use period. The Houyi trial, which involved Chinese ACS patients, revealed that ticagrelor significantly increased the inhibition of platelet aggregation (IPA) at 0.5, 2, 8 and 24 hours and at six weeks after intervention, when compared with clopidogrel. In the ticagrelor group, IPA at two hours after intervention was 4.9 times (48.2% *vs*. 9.8%) of that in the clopidogrel group. Furthermore, the proportion of patients with a number of 24-hour P2Y12 reaction units (PRU) of < 240 was 100% in the ticagrelor group and 75.9% in the clopidogrel group [6]. The results of the present study were basically consistent with the results of the Houyi trial, where ticagrelor had a stronger inhibition effect on platelet aggregation, compared with clopidogrel. For the improvement of LVEF and LVEDD, the results of the present study were consistent with those reported in a literature [25], which all proved that ticagrelor was more effective in improving LVEF and LVEDD, compared with clopidogrel. However, the present study focused more on the comparison of these two indicators at one year after the intervention, in which the recovery level was more significantly improved in the ticagrelor group than in the clopidogrel group.

The Chinese Expert Consensus Statement on the Clinical Use of Ticagrelor points out that [8] when bleeding occurs, proper supportive treatment measures should be taken. In particular, attention should be given to local hemostasis after determining the cause of bleeding and controlling the bleeding, and ticagrelor can be reused. Dyspnea is a common adverse reaction to ticagrelor, which may be correlated to the increase in plasma adenosine concentration. A Chinese study revealed that the incidence of dyspnea was higher in the ticagrelor group than in the clopidogrel group, which mostly occurred within one month after the administration of the drug. These were mostly were mild, mostly complicated with chronic obstructive pulmonary disease, to which patients could tolerate, and no drug withdrawal occurred [26]. According to the results of the present study, the monitoring of medicine safety in these two groups revealed that minor bleeding events and dyspnea occurred in both groups, and the difference in minor bleeding events between the two groups was statistically significant. The risk was higher in the ticagrelor group than in the clopidogrel group. Furthermore, the difference in the total incidence between these two groups was statistically significant, but no drug withdrawal or medication change caused by adverse reactions was observed.

In summary, the present study revealed that compared with the clopidogrel, the incidence of MACE was more significantly decreased when ticagrelor was given to AMI patients who underwent emergency PCI, and the application of ticagrelor had advantages of improving the recovery levels of LVEF, LVEDD and platelet inhibition. For drug safety, the incidence of minor bleeding events was higher in the ticagrelor group than in the clopidogrel group, and the incidence of overall adverse events was higher in the ticagrelor group than in the clopidogrel group. However, no drug withdrawal or medication change caused by adverse reactions was observed. Attention should be given to these adverse reactions. Overall, for AMI patients treated with emergency PCI, ticagrelor has a relatively satisfactory clinical efficacy and relative safety, when compared to clopidogrel.

Acknowledgements

We are particularly grateful to all the people who have given us help on our article. Fund Project: The task book of Hebei science and technology project (ID: 16277780D).

Disclosure of conflict of interest

None.

Address correspondence to: Rong-Pin Du, Department of Cardiology, Hebei General Hospital, No.

348, Peace West Road, Shijiazhuang 050000, Hebei, China. Tel: +86 15128138630; Fax: +86 0311-85989696; E-mail: durp_as@163.com

References

[1] National Health and Family Planning Commission. China's annual statistical yearbook for health and family planning 2016. Beijing: Peking Union Medical College press; 2016.

[2] Chen FY. Treatment of acute ST segment elevation myocardial infarction and guidelines for percutaneous coronary intervention in China. Chinese Journal of Emergency Medicine 2016; 25: 857-861.

[3] Samoš M, Šimonová R, Kovář F, Duraj L, Fedorová J, Galajda P, Staško J, Fedor M, Kubisz P, Mokáň M. Clopidogrel resistance in diabetic patient with acute myocardial infarction due to stent thrombosis. Am J Emerg Med 2014; 32: 461-465.

[4] Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, TenBerg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D, Marcucci R, Reny J, Trenk D, Sibbing D, Gurbel PA; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013; 62: 2261-2273.

[5] Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009; 120: 2577-2585.

[6] Chen Y, Dong W, Wan Z, Li Z, Cong H, Hong T, Yin T. Ticagrelor versus clopidogrel in Chinese patients with acute coronary syndrome: a pharmacodynamic analysis. Int J Cardiol 2015; 201: 545-546.

[7] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-1057.

[8] Chinese Medical Doctor Association cardiovascular physician branch thrombus prevention and control Specialized Committee, Interventional group of cardiovascular branch of Chinese Medical Association, Editorial Committee of the Chinese Journal of cardiovascular disease, et al. Chinese expert consensus on the clinical application of ticagrelor. Clin J Med Offic 2016; 44: 444-453.

[9] Yang YH, Sun X, Tian Y. Advances in the study of the biological effects of the ticagrelor. Journal of Clinical Cardiovascular Disease 2015; 31: 122-124.

[10] Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J 2016; 37: 3232-3245.

[11] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Kardiol Pol 2018; 76: 229-313.

[12] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G,Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791-1800.

[13] Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG,Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014; 371: 2155-2166.

[14] Kim C, Shin DH, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, Park J, Lee H, Choi YJ, Choi YS, Oh SK, Jang Y. The use pattern and clinical impact of new antiplatelet agents including prasugrel and ticagrelor on 30-day outcomes after acute myocardial infarction in Korea: Korean health insurance review and assessment data. Korean Circ J 2017; 47: 888-897.

[15] Tang XF, Wang J, Zhang JH, Meng XM, Xu B, Qiao SB, Wu YJ, Chen J, Wu Y, Chen JL, Gao RL, Yuan JQ, Yang YJ. Effect of the CYP2C19 2 and 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 2013; 69: 1103-1112.

[16] Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, Ikeda T, Kurihara A. Identification of the human cytochrome P450 en-

zymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos 2010; 38: 92-99.

[17] Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA, Bach RG. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. Circ Cardiovasc Genet 2014; 7: 277-286.

[18] Zhong SL, Han YL, Chen JY, Yuan JQ, Sun YH, Wang XZ, Li Y. Interpretation of genotyping guide for individual drug use in clopidogrel antiplatelet therapy. Chinese Journal of Practical Internal Medicine 2015; 35: 38-41.

[19] Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC; PLATO Investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010; 376: 1320-1328.

[20] Mahaffey KW, Held C, Wojdyla DM, James SK, Katus HA, Husted S, Steg PG, Cannon CP, Becker RC, Storey RF, Khurmi NS, Nicolau JC, Yu CM, Ardissino D, Budaj A, Morais J, Montgomery D, Himmelmann A, Harrington RA, Wallentin L; PLATO Investigators. Ticagrelor effects on myocardial infarction and the impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2014; 63: 1493-1499.

[21] Perl L, Zemer-Wassercug N, Rechavia E, Vaduganathan M, Orvin K, Weissler-Snir A, Lerman-Shivek H, Kornowski R, Lev EI. Comparison of platelet inhibition by prasugrel versus ticagrelor over time in patients with acute myocardial infarction. J Thromb Thrombolysis 2015; 39: 1-7.

[22] Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, Held P, Jensen EC, Sabatine MS. Design and rationale for the prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infarction 54 (PEGASUS-TIMI 54) trial. Am Heart J 2014; 167: 437-444, e5.

[23] 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: 4636-41.

[24] Varenhorst C, Alström U, Scirica BM, Hogue CW, Åsenblad N, Storey RF, Steg PhG, Horrow J, Mahaffey KW, Becker RC, James S, Cannon CP, Brandrup-Wognsen G, Wallentin L, Held C. Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. J Am Coll Cardiol 2012; 60: 1623-1630.

[25] Ma XR, Cheng RC, Xue L, Tian JW, Li XQ. The effect of myocardial perfusion level on cardiac function and left ventricular remodeling in patients with AMI after PCI. Heart Magazine 2013; 25: 190-193.

[26] Li ZH, Zhang YC, Xie YQ, Zhang Y, Xu CH, Xiang Y, Wu H, Chen MT, Meng S, Shen CX. Observation of the efficacy and safety of trailer in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Chinese Journal of Interventional Cardiology 2015; 23: 2-4.