## Original Article
# Analysis of antiplatelet activity and short-term prognosis of ticagrelor in AMI patients undergoing emergency PCI during perioperative period

Zongqin Yao[1], Guangfeng Li[2], Cunyu Fu[1], Guangcai Li[3]

*Departments of [1]Cardiovascular Medicine, [2]Neurology Medicine, [3]Pharmacy, Linyi Central Hospital, Linyi, Shandong, China*

**Abstract:** Objective: To evaluate the antiplatelet activity efficiency and the short-term prognoses of ticagrelor in patients who had acute myocardial infarction (AMI) and suffered emergency percutaneous coronary intervention (PCI), in the perioperative period. Methods: 120 subjects were selected from AMI patients underwent emergency PCI in our hospital, and randomized into two groups: clopidogrel group and ticagrelor group, with 60 cases in each group. Then, patients in these two groups were administered orally with clopidogrel and aspirin, ticagrelor and aspirin in perioperative period, respectively. Before PCI, and 24 h, 48 h after surgery, the differences of the parameters of thrombelastogram (TEG) (including R value, K value, α angle, MA value and CI value) betweentwo groups' patients were measured and compared respectively. Meanwhile, a comparison was performed to analyse the different of the rate of maximum platelet aggregation induced by adenosine diphosphate (MARADP) and arachidonic acid (MARAA). After six months follow-up, the incidences of major adverse cardiac events (MACE) and bleeding events of two groups were compared. Results: Compared with the preoperative values, postoperative R value, K value, MARAA and MARADP of both groups were all apparently higher with statistical significance, while α angle, MA value and CI value were evidently decreased ($P<0.05$). Conversely, at 24 and 48 h after surgery, there was no significant difference ($P>0.05$). Compared to clopidogrel group, the high levels of R value, K value, MARAA and MARADP in ticagrelor group could be observed at all time points ($P<0.05$), while a significant reduction of α angle, MA value and CI value could be figured out ($P<0.05$). After six-month follow-up, the occurrence of total MACE and bleeding events in ticagrelor group were apparently lower than that of clopidogrel group ($P<0.05$). Conclusion: Ticagrelor could remarkably improve antiplatelet activity efficiency for AMI in emergency PCI during perioperative period, and decrease the incidence of short-term MACE without raising the risk of bleeding.

**Keywords:** Ticagrelor, acute myocardial infarction, PCI, thrombelastogram, major adverse cardiac events, prognosis

## Introduction

Acute myocardial infarction (AMI) is a common cardiovascular emergency in clinical, and its pathology basis is the rupture of instability plaque on arteria coronaria, leading to the formation of acute thrombosis which could entirely or mostly clog the main branches of coronary, resulting in the acute myocardial ischemia. Hence, platelet activation acts as a key factor in this pathological process [1, 2]. Currently, clinical guidelines in the world all suggest intensive antiplatelet therapy as basic treatment for AMI, especially for patients who underwent emergency PCI, which is recognized as the most effective method for revascularization, should be treated with clopidogrel and aspirin for dual antiplatelet therapy in the perioperative period [3-5]. However, the clinical feature in recent years have indicated that there are lots of limitations on the antiplatelet effect of clopidogrel. It not only has large variability in human response, but effects slowly, which is also known as "clopidogrel resistance" [6-11]. Ticagrelor, a novel adenosine diphosphate (ADP) receptor antagonist, has stronger antiplatelet feature and faster onset compared to clopidogrel. Therefore, another research suggested that for AMI patients undergoing emergency PCI, they could taketicagrelor and aspirin in

**Table 1.** Comparison of patients' general information (n=60)

| Clinical indexes | Clopidogrel group | Ticagrelor group | $t/\chi^2$ | P value |
|---|---|---|---|---|
| Age (years old) | 59.8±10.8 | 60.4±12.7 | 1.678 | 0.379 |
| Sex ratio (male:female) | 36:24 | 38:22 | 4.326 | 0.138 |
| BMI (kg/m$^2$) | 23.3±2.7 | 24.1±3.0 | 1.820 | 0.147 |
| Hyperlipidemia history (%) | 43.3 (26/60) | 41.7 (25/60) | 6.023 | 0.098 |
| Hypertension history (%) | 51.7 (31/60) | 55.0 (33/60) | 6.189 | 0.087 |
| Diabetes history (%) | 45.0 (27/60) | 46.7 (28/60) | 5.841 | 0.126 |
| Smoking history (%) | 65.0 (39/60) | 61.7 (37/60) | 6.166 | 0.088 |
| History of taking aspirin (%) | 76.7 (46/60) | 73.3 (44/60) | 6.257 | 0.084 |
| History of taking statins (%) | 63.3 (38/60) | 66.7 (40/60) | 6.125 | 0.091 |
| History of taking ACEI/ARB | 60.0 (36/60) | 58.3 (35/60) | 6.359 | 0.080 |
| LDL-C (mmol/L) | 2.18±0.49 | 2.23±0.56 | 1.824 | 0.107 |
| TC (mmol/L) | 4.28±0.78 | 4.14±0.82 | 1.759 | 0.131 |
| FBG (mmol/L) | 6.72±0.89 | 6.62±1.02 | 1.585 | 0.188 |
| SCr (μmol/L) | 86.9±10.8 | 85.5±12.7 | 1.516 | 0.202 |
| PT (s) | 12.53±0.76 | 12.79±0.66 | 1.518 | 0.201 |
| APTT (s) | 36.86±4.49 | 37.91±5.13 | 1.633 | 0.181 |

perioperative period for better antiplatelet activity efficiency and prognosis [12]. Concerning the very few clinical reports about this treatment, our study is aimed to compare the antiplatelet efficiency of ticagrelor and clopidogrel via analyzing the clinical data of AMI patients undergoing emergency PCI in perioperation. The reports are as follows.

**Clinical materials and methods**

*Subjects*

120 hospitalized AMI patients undergoing emergency PCI in our hospital from January 2015 to June 2016 were enrolled as subjects, including 74 males and 46 females, aging 47-72 with average age of 60.2±12.3. All patients and their families have provided informed consent. This study has been approved by the Ethics Committee in our hospital. Inclusion criteria: patients whose symptoms were in accordance with the diagnosis criteria of the guideline from American Heart Association for acute myocardial infarction published in 2000; patients who are younger than 75 years old; patients who had received emergency PCI and followed up according to medical order with complete clinical data; patients took neither anticoagulants like warfarin or others, nor antiplatelet medication like clopidogrel and ticagrelor within a week. Exclusion criteria: patients

who had severe cardiogenic shock and cardiac insufficiency; patients who had took anticoagulant like warfarin within a week; patients who were complicated others diseases such as severe coagulation disorders, moderate or severe anemia, active peptic ulceration, intracerebral hemorrhage, therioma, etc.; patients who were allergic to aspirin, clopidogrel and ticagrelor.

*Grouping*

A total of 120 subjects were randomly divided into two groups according to random number table. Clopidogrel group (60 cases): took clopidogrel and aspirin orally in perioperative period, including 36 males and 24 females with the average age of 59.8±10.8. Ticagrelor group: took ticagrelor and aspirin orally in perioperative period as 38 subjects were male while 22 subjects were female with the average age of 60.7±12.7. The age, sex, primary diseases and other parameters had no statistical difference (P>0.05), indicating the data about the antiplatelet efficiency of clopidogrel and ticagrelor on patients were comparable (see **Table 1**).

*Treatments*

In this study, all patients have performed emergency PCI in line with clinical guideline, and at the same time, received the basic treatments for AMI, including aspirin, atorvastatin, isosorbide mononitrate, metoprolol and so forth every day. After PCI, they were all hypodermic injected with enoxaparin sodium (brand name: clexane, brought from Sanofi-Aventis Co. Ltd., license number: H20100484) for anticoagulation.

Before the emergency PCI surgery, a loading dose of clopidogrel (Sanofi-Aventis Co. Ltd.) 600 mg and aspirin (Bayer AG) 300 mg were administered orally for AMI patients in clopidogrel group. After the PCI surgery, patients kept taking clopidogrel 75 mg qd and aspirin 100 mg qd orally.

**Table 2.** Comparison of platelet functions of two groups (n=60)

| Group | Time point | R (s) | K (s) | α angle | MA (mm) | CI value | MARAA (%) | MARADP (%) |
|---|---|---|---|---|---|---|---|---|
| Clopidogrel group | Before surgery | 16.9±2.4 | 10.2±1.5 | 36.2±3.2 | 44.8±4.3 | -(3.8±0.4) | 49.3±2.0 | 36.9±2.4 |
| | 24 h | 21.7±2.9 | 13.6±1.2 | 33.1±2.3 | 41.2±3.9 | -(4.4±0.3) | 65.4±3.9 | 45.7±4.6 |
| | 48 h | 22.1±2.0 | 13.2±0.9 | 33.5±2.4 | 40.7±2.7 | -(4.3±0.5) | 65.8±2.8 | 46.2±5.0 |
| | F value | 9.384 | 9.424 | 9.005 | 9.016 | 9.203 | 9.987 | 9.902 |
| | P value | 0.028 | 0.024 | 0.040 | 0.039 | 0.031 | 0.007 | 0.010 |
| Ticagrelor group | Before surgery | 18.0±2.7[a] | 11.9±1.5[a] | 32.5±2.7[a] | 39.5±3.6[a] | -(4.2±0.3)[a] | 58.4±4.3[a] | 39.3±4.7[a] |
| | 24 h | 23.6±2.2[b] | 15.4±2.1[b] | 28.4±1.4[b] | 38.3±3.2[b] | -(4.9±0.5)[b] | 71.6±4.2[b] | 50.6±5.2[b] |
| | 48 h | 24.2±2.6[c] | 14.9±1.2[c] | 27.8±1.9[c] | 37.9±3.1[c] | -(5.0±0.4)[c] | 71.1±3.6[c] | 52.2±4.6[c] |
| | F value | 9.576 | 9.886 | 9.254 | 8.986 | 9.502 | 10.024 | 10.225 |
| | P value | 0.020 | 0.011 | 0.030 | 0.041 | 0.021 | 0.006 | 0.003 |

Note: compared with the clopidogrel group, [a]P<0.05, [b]P<0.05, [c]P<0.05; 24 h, 24 h after surgery; 48 h, 48 h after surgery.

Before the emergency PCI surgery, a loading dose of ticagrelor (AstreZeneca, AB) 180 mg and aspirin (Bayer, AG) 300 mg were administered orally for AMI patients in ticagrelor group. After the PCI surgery, patients kept taking ticagrelor 90 mg qd and aspirin 100 mg qd orally.

*Test of thrombelastogram (TEG)*

*Main parameters tested:* The coagulation analyzer (produced by Haemoscope America Co., TEG 5000) was adopted for thrombelastography (TEG) examination before PCI, and 24 h and 48 h after it. The sample, venous blood, which was collected in the blood taking pipe with anticoagulaut of EDTA-2Na and then tested following the instructions within 2 h. R value, K value, α angle, MA value and CI value are main detecting parameters R value refers to reaction time; K value is the time from the end of reaction until the clot reaches 20 mm; α angle is defined as the angle between horizontal line and the tangent of the biggest curve made from the formation point of colt in TEG; MA is maximum amplitude; CI represents the integrative coagulation index which can indicate the comprehensive condition of coagulation under varies experimental conditions and when the value is lower than -3, it represents hypocoagulability, while if the value is higher than +3, it means hypercoagulability, otherwise it indicates normal.

*Maximum platelet aggregation*

Detect the maximum platelet aggregation through 1 mol/L AA (MARAA) and 2 μmol ADP (MARADP) before PCI, and 24 h and 48 h after it.

*Record of major adverse cardiac events and bleeding events*

All patients were followed up for 6 months with 1-month intervals after they came out. Major adverse cardiac events (MACE) and bleeding events were recorded for calculating their incidences respectively. MACE contained restenosis of target vessel and non-target vessel, thrombosis, recurrent angina, second myocardial infarction, all-cause death and so forth. Bleeding events referred to the standard defined by Bleeding Academic Research Consonium (BARC).

*Statistical analysis*

This study applied statistical software SPSS 15.0, and the measurement data were expressed as mean ± standard deviation, while t test were used to compare the patients' general information of two groups. ANOVA was adopted for the comparison of parameters of TEG at each time points, while SNK test was conducted for the comparison between two groups. Count data were expressed in percentage and analyzed by $\chi^2$ test. P<0.05 was considered as statistically significant difference.

**Results**

*Comparison of the general information in two groups*

In comparison with clopidogrel group, the age, sex ratio, primary disease, smoking history, medication history and biochemical indicators had no statistically significant difference (all P>0.05) (see **Table 1**).

**Table 3.** Comparison of incidence of MACE of two groups (n=60, %)

| Group | Second PCI | Recurrent angina | Second myocardial infarction | All-cause death | Total incidence of MACE |
|---|---|---|---|---|---|
| Control group | 8.3 (5/60) | 13.3 (8/60) | 10.0 (6/60) | 1.7 (1/60) | 33.3 (20/60) |
| Observation group | 5.0 (3/60) | 8.3 (5/60) | 5.0 (3/60) | 0.0 (0/60) | 18.3 (11/60) |
| $\chi^2$ value | 10.638 | 11.587 | 12.006 | 23.688 | 11.612 |
| P value | 0.023 | 0.019 | 0.016 | 0.001 | 0.020 |

**Table 4.** Comparison of incidence of bleeding events of two groups (n=60, %)

| Group | Type 1 | Type 2 | Type 3 | Type 5 |
|---|---|---|---|---|
| Clopidogrel group | 38.3 (23/60) | 1.7 (1/60) | 0.0 (0/60) | 0.0 (0/60) |
| Ticagrelor group | 16.7 (10/60) | 0.0 (0/60) | 0.0 (0/60) | 0.0 (0/60) |
| $\chi^2$ value | 12.351 | 23.688 | - | - |
| P value | 0.012 | 0.001 | - | - |

Note: Type 1: Non-active bleeding events; Type 2: Active bleeding events; Type 3: Intracranial hemorrhage or cardiac tamponed; Type 5: Fatal bleeding events.

*Comparison of platelet functions of two groups*

The value of R, K, MARAA and MARADP before the operation were all significantly higher than that after the operation (P<0.05), while the α angle, MA value and CI value were obviously decreased (P<0.05). Meanwhile, there was no obvious difference observed at 24 and 48 hours after the surgery (P>0.05).

In comparison with the clopidogrel group, the preoperative and postoperative values of R, K, MARAA and MARADP at all time points of ticagrelor group were all significantly higher (P<0.05), while the α angle, MA value and CI value were obviously decreased (P<0.05) (see **Table 2**).

*Comparison of short-term prognoses of two groups*

After six-month follow-up, ticagrelor group maintained lower incidences of varies ischemic events and the total MACE than that of clopidogrel group, the difference was statistically significant (see **Tables 3**, **4**). No severe or fatal bleeding events which ranked level 3 or above in the standard of BARC, happened during the follow-up period, except one case of gastrorrhagia with blood loss exceeding 800 ml in clopidogrel group, whose symptoms improved after hemostasis and blood transfusion. Subjects in ticagrelor group had apparently lower incidences of non-active and active bleeding events than that of clopidogrel group (P<0.05) (see **Table 4**).

**Discussion**

In this study, we detected the parameters of TEG to evaluate the activity of plateletin AMI patients who received PCI during perioperative period of these two groups, and the results confirmed that patients' platelet activity before PCI was significantly lower than that's at other postoperative time points, indicating a preferable clinical effect could be carried out via the dual antiplatelet therapies of clopidogrel combined with aspirin or ticagrelor combined with aspirin. Meanwhile, the platelet activity was indicative of no significant difference between 24 h and 48 h after surgery, which suggested that the duration of these two kinds of antiplatelet therapies was satisfying. The further analysis of TEG showed that at the same time point, the values of R and K in ticagrelor group were considerably higher compared to clopidogrel group, while α angle, MA value and CI value were obviously lower, suggesting that the antiplatelet activity of ticagrelor combined with aspirin was clearly superior to that of clopidogrel combined with aspirin. This finding was consistent with the previous studies [13, 14]. Moreover, MARAA and MARADP of ticagrelor group were relatively higher, and a study has proved that the platelet inhibition rate induced by ADP (MARADP) which was detected by TEG test, was negatively related to the restenosis after PCI [15]. Besides, CREST research has proved that the risk of hemorrhagic and ischemic events and stent thrombosis of AMI patients could be correspondingly higher with the increasing of the residual platelet activity after antiplatelet therapy [16]. Hence, ticagrelor had better therapeutic effect than clopidogrel. Recently, ONSET/

OFFSET's study also indicated that compared with clopidogrel, ticagrelor showed stronger antiplatelet effect, shorter onset time and quicker recovery for platelet aggregation after drug discontinuance [17]. Furthermore, the study of RESPOND, similarly, verified that even on patients who had no respond or resistance to clopidogrel, applying ticagrelor can still inhibit platelet effectively [18]. Some other studies also pointed out that ticagrelor can validly reduce the high residual platelet activity after taking clopidogrel [19].

During six-month follow-up, the rates of ischemic events and total MACE in ticagrelor group were all markedly lower than that of clopidogrel group, revealing that ticagrelor combined with aspirin was more effective. Meanwhile, the prevalence of bleeding events in ticagrelor group was significantly lower than that of clopidogrel group and there was no severe or fatal bleeding events in both of groups, which meant ticagrelor combined with aspirin for antiplatelet therapy was safer. In the recent PLATO study, researchers also proved that compared with clopidogrel, ticagrlor can further decrease the risk of relapsing ischemic events in AMI patients, thereby notably lower the all-cause mortality without any significant raising in occurrence of bleeding events [20]. Therefore, ticagrelor was considered to have good clinical outcomes, apparent safety, and obvious decline in the recurrence rate of MACE and the total mortality of AMI patients. So it had been recommended by many clinical guidelines (Ib).

Among all the patients in the two groups, we compared their basic parameters such as age, sex ratio, primary diseases, smoking history, medication history, biochemical indicators and etc. The results showed no statistical difference, indicating a well randomization and no evident systematic bias. On the basis of it, this study confirmed that ticagrelor administration for AMI patients after emergency PCI in perioperative period can significantly inhibit platelet activity and improve the short-term prognosis, and its effect was superior to clopidogrel, so as to provide a better evidence-based guideline in clinical treatment for AMI patients. However, due to the comparatively small sample size and short follow-up period, it cannot be sure whether continuously taking ticagrelor after the surgery has the same effects on long term progno-

sis for AMI patients undergoing PCI. So it still need subsequent clinical researches to evaluate it.

In conclusion, ticagrelor can significantly improve the antiplatelet efficiency in perioperative period of AMI patients undergoing emergency PCI, and reduce the incidence of short-term MACE without increasing the risk of bleeding. Compared with clopidogrel, ticagrelor had a preferable therapeutic effect and a good application prospect for clinical AMI treatment.

**Disclosure of conflict of interest**

None.

**Address correspondence to:** Guangcai Li, Department of Pharmacy, Linyi Central Hospital, No. 17 Jiankang Road, Yishui, Linyi 276400, Shandong, China. Tel: +86-0539-2251934; E-mail: liguangcai1738@163.com

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