Comparison of Ticagrelor with Clopidogrel in Reducing Interleukin-17 and Myeloperoxidase Expression in Thrombus and Improving Postprocedural Coronary Flow in ST-segment Elevation Myocardial Infarction Patients

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ABSTRACT - Purpose. This study aimed to explore the effects of ticagrelor (a P2Y12 receptor inhibitor) on interleukin (IL)-17 and myeloperoxidase (MPO) expression in coronary thrombus as well as on the coronary blood flow in ST-segment elevation myocardial infarction (STEMI) patients following percutaneous coronary intervention (PCI).

Methods. Forty STEMI patients who were admitted to the First Affiliated Hospital of Harbin Medical University between August 1, 2014 and December 30, 2014 were enrolled in this study according to a set inclusion criteria. They were randomized to ticagrelor and clopidogrel groups and treated with 180 mg ticagrelor and 600 mg clopidogrel before PCI, respectively. Intracoronary thrombus aspiration was performed by a physician during PCI. Immunohistochemistry and Western blot analysis were carried out to detect the expression of IL-17 and MPO in the thrombus. Corrected thrombolysis in myocardial infarction frame count (CTFC) was used to evaluate blood flow after PCI.

Results. Immunohistochemistry results showed that the average positive staining area percentage of IL-17 and MPO in the clopidogrel group was significantly higher than that in the ticagrelor group. Western blot analysis also showed similar results for IL-17 (clopidogrel 0.71 ± 0.036, ticagrelor 0.50 ± 0.56) and MPO (clopidogrel 0.50 ± 0.040; ticagrelor 0.38 ± 0.06). CTFC was lower in the ticagrelor group than that in the clopidogrel group (P < 0.05). Conclusions. Ticagrelor is more effective than clopidogrel in reducing inflammation thrombosis and improving postprocedural PCI blood flow in STEMI patients.

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INTRODUCTION

Acute coronary syndrome (ACS) usually results from one of the following three problems: unstable angina (38%), ST-segment elevation myocardial infarction (STEMI, 30%), or non-ST-segment elevation myocardial infarction (25%) (1). In the United States, approximately 780,000 people receive a diagnosis of ACS and 17,255 receive a diagnosis of STEMI annually (2, 3). Emergency primary percutaneous coronary intervention (PCI) is currently the primary treatment of choice for STEMI (4) because the coronary artery can be quickly opened to prevent cardiomyocyte necrosis. However, after PCI, STEMI still exhibits a prothrombotic state due to platelet activation (5). The activated platelets play an important role in coronary atherosclerosis and ACS by adhering to the endothelial cells, aggregating in the vascular wall, and releasing platelet granules to induce chronic coronary atherosclerotic plaque rupture, thrombus formation, vascular occlusion, and blood flow change (6, 7). Platelet activation is mediated by G-protein coupled adenosine diphosphate (ADP) receptors P2Y1 and P2Y12 (8). P2Y12 is reported to play a vital role in platelet aggregation (9). Therefore, P2Y12 inhibitors or P2Y12 receptor antagonists may be pivotal in the treatment of ACS. Dual-antiplatelet therapy with aspirin and thienopyridines (prasugrel, ticlopidine, and clopidogrel), which bind to P2Y12 receptors, has shown great efficacy in the treatment of patients with ACS (10, 11).

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Clopidogrel is a classic antiplatelet drug and irreversible P2Y12 antagonist. Ticagrelor, a novel oral P2Y12 receptor antagonist, can reversibly bind to P2Y12 receptor without undergoing biotransformation (12). A Platelet Inhibition and Patient Outcomes study proved that compared with clopidogrel, ticagrelor is more effective in reducing major adverse cardiac events, cardiovascular mortality, and all-cause mortality in patients with STEMI after the administration of low-dose aspirin (13). Several studies attribute the pathogenesis of STEMI to the thrombotic complications induced by atherosclerosis. However, in 2013, Libby suggested that inflammation plays a crucial role in ACS (14). Inflammatory cell infiltration can promote plaque rupture and accelerate thrombosis (15, 16). Thus, the administration of anti-inflammatory agents following PCI is critical for STEMI patients. However, the effect of ticagrelor on inflammatory cell infiltration in thrombus is unclear.

Interleukin (IL)-17 and myeloperoxidase (MPO) are two inflammatory biomarkers in ACS (17). IL-17 is produced by unconventional T cells and appears to regulate local tissue inflammation via the coordinated expression of chemokines and proinflammatory cytokines. Recent animal studies suggested the pro-atherogenic role of IL-17 (18, 19). IL-17 is highly expressed in patients with coronary and symptomatic carotid atherosclerotic lesions, which can induce the production of pre-inflammatory mediators (20). Released from the human polymorphonuclear neutrophils, MPO has been suggested to play an important role in inflammatory vascular diseases (21). Therefore, we clinically investigated the effects of ticagrelor on IL-17 and MPO expression in coronary artery thrombus and the blood flow change in STEMI patients with PCI, relative to clopidogrel.

**MATERIALS AND METHODS**

This study was approved by the Ethics Committee of the First Hospital of Harbin Medical University. All patients provided written informed consent.

**Patients**

The participants for this study were selected from a group of individuals reported with acute STEMI from April 1, 2014 to December 30, 2014 at the Cardiology Department of the First Hospital of the Harbin Medical University, Harbin, China. The inclusion criteria for this study were as follows: 1) the participants were women who were not in the gestation period or men; 2) age range of 18–79 years; 3) persistence of myocardial infarction symptoms for more than 30 min; 4) arrival at the hospital within 24 h after the onset of chest pain; 5) the ST segment was the elevation at the admission time; and 6) patients who were intended to receive emergency PCI. Additionally, before admission, patients would be asked in detail whether they took acetylsalicylic acid (aspirin). If the patient regularly took acetylsalicylic acid (aspirin) before admission, he or she would not be given acetylsalicylic acid (aspirin) before operation. If the patient did not take aspirin, he (she) would be given loading dose (300 mg) of acetylsalicylic acid (aspirin) to rule out the impact of aspirin.

However, the exclusion criteria were as follows: patients 1) who had accepted P2Y12 receptor antagonist treatment within the past 30 days; 2) who were allergic to clopidogrel or ticagrelor; 3) who had administered oral anticoagulants; 4) who used platelet IIb/IIIa inhibitors within the past 7 days; 5) who had a history of intracranial hemorrhage; and 6) who had severe cardiac or renal insufficiency.

**Random allocation**

According to the inclusion and exclusion criteria, 40 acute STEMI patients, including 25 men and 15 women were enrolled in this study. They were randomly divided into two groups according to the treatment regimens as follows: ticagrelor (n = 20) and clopidogrel groups (n = 20). Before PCI, the patients in the ticagrelor group were orally administered ticagrelor (loading dose, 180 mg) and aspirin (loading dose, 300 mg), while patients in the clopidogrel group were administered clopidogrel (loading dose, 600 mg) and acetylsalicylic acid (aspirin) (loading dose, 300 mg).

All patients underwent venous blood tests for hypersensitive C-reactive protein (HsCRP), and routine blood tests for blood lipid, random blood glucose, myocardial enzymes, and myocardial calcium protein I (TnI). The hemodynamics of the coronary artery after emergency PCI was observed by three cardiologists who were blinded to the administration of the drugs. The corrected thrombolysis in myocardial infarction frame count (CTFC) was recorded.

**PCI procedures**

First, a radial artery sheath was placed through the radial artery. Under the guidance of a loach guide wire, the angiography catheter was loaded in the coronary ostium of the left and right coronary arteries through the radial artery sheath. Culprit
vessels were found through coronary radiography. Next, thrombus aspiration was performed to remove the thrombus and open the vessels. A stent was applied if there was 75% or more stenosis, while the procedure was ended if there was < 75% stenosis. The procedure of thrombus aspiration was as follows: a catheter was loaded under the guidance of a guide wire. The guide wire was introduced into the vessel lumen at the distal end of the stenosis via a catheter for repeated suction. During the procedure, radiography was performed to check whether the thrombus was clearly aspirated (22).

**Pathological section**

Thrombus aspiration in the coronary artery of STEMI patients during PCI is shown in Figure 1. The thrombus was washed with normal saline and stored in 4% paraformaldehyde solution. Six hours later, the tissues were dehydrated with a graded series of sugar solution (10, 20, and 30%). During this process, sugar solution at higher concentration was added when the tissue samples were deposited in a sugar solution of lower concentration. The samples were repeatedly rinsed with water, and then dehydrated in graded ethanol solutions (50–100%). The samples were cleared twice in xylene solution for 0.5 h till hyaline and then embedded in paraffin. The tissues were then sliced into 5 μm sections.

**Immunohistochemistry**

For immunohistochemical staining, paraffin-embedded sections were baked at 60°C for 120 min and dewaxed in xylene solution. The sections were hydrated in graded ethanol solutions followed by incubation with 3% hydrogen peroxide (H₂O₂) for 30 min at room temperature to block the activity of endogenous peroxidases. Antigen retrieval was performed by heating in a microwave oven. The sections were then incubated with primary antibodies (IL-17 antibody and MPO antibodies, Abcam, USA) at 4°C overnight. After washing in phosphate-buffered saline (PBS) three times, the secondary antibody was added and incubated at 37°C for 30–60 min. The sections were developed with DAB. Then, they were counterstained with hematoxylin, dehydrated, hyalinized, and mounted. After drying, the sections were observed under IX70 optical microscope (Olympus, Tokyo, Japan). The positively stained area was claybank. Five random positive fields were selected for the quantification of the average positive staining area percentage (APSAP) (23).

**Western blot**

The thrombus tissues (50 mg) were pulverized and lysed in 30–50 μL lysis buffers for 30 min on ice. They were centrifuged (12,000 rpm, 4°C, 5 min), and the supernatant was used for protein quantification by using BCA kit. The samples with 30 μg proteins were loaded onto sodium dodecyl sulphate polyacrylamide gel (SDS-PAGE). The proteins were transferred from the gel to a membrane, stained with Ponceau, and blocked. The membrane was incubated with primary antibodies (anti-IL-17 and anti-MPO antibodies, abcam, USA). Then, the secondary antibody was added, followed by exposure, development, and fixing. The bands were analysed by Image Pro Plus software. β-actin was used as an internal reference (24).

**STATISTICAL ANALYSIS**

All statistical analyses were performed using SPSS 19.0 software (Chicago, IL, USA). Data were presented as the mean ± standard deviation (SD). Measurement data were analysed using Student's *t*-test, while numeration data (clinical data) were analysed by χ² test. *P* < 0.05 was defined as statistically significant.

**RESULTS**

**Characteristics of STEMI patients**

The characteristics of 40 STEMI patients are listed in Table 1. There was no statistical difference in basic clinical data, including sex, age, duration of chest pain symptoms, time between the oral drugs and PCI, reperfusion time, preprocedural oral statins, preprocedural low molecular heparin/common heparin, history of hypertension, diabetes, smoking, and old myocardial infarction, as well as laboratory data (HsCRP, WBC, neutrophilic granulocyte percentage, absolute neutrophil count, monocyte number, neutrophils/lymphocytes, random blood sugar) between the clopidogrel and ticagrelor groups. In addition, there was no significant difference in postprocedural clinical data, such as Killip, ejection fraction, culprit vessel-related factors, blood lipid, preprocedural cardiac enzyme, postprocedural blood, and postprocedural cardiac enzyme between the two groups (Table 2).
Table 1  Characteristics of ST-segment elevation myocardial infarction (STEMI) patients.

| Clinical characteristics                  | Clopidogrel (n=20) | Ticagrelor (n=20) | P  |
|-------------------------------------------|--------------------|-------------------|----|
| Male                                      | 13 (65%)           | 12 (60%)          | 0.74|
| Age (years)                               | 59.45± 10.98       | 58.54± 16.48      | 0.88|
| Relevant cardiovascular risk factors       |                    |                   |    |
| Hypertension history                       | 11 (55%)           | 10 (50%)          | 0.75|
| Diabetes history                           | 7 (35%)            | 8 (40%)           | 0.74|
| Smoking history                            | 12 (60%)           | 10 (50%)          | 0.52|
| OMI history                               | 4 (20%)            | 5 (25%)           | 0.70|
| Duration of chest pain symptoms, h        | 2.81± 0.78         | 2.63± 0.86        | 0.71|
| Orally administered drugs to the time of PCI, min | 85.27±15.67        | 80.81±18.84       | 0.11|
| Reperfusion time, min<sup>1</sup>         | 289±89.05          | 284±74.07         | 0.66|
| Preprocedural oral statins<sup>2</sup>    | 18 (90%)           | 17 (85%)          | 0.63|
| Preprocedural low molecular heparin/common heparin | 12 (60%)           | 14 (70%)          | 0.50|
| Laboratory data (preoperative urgent inspection) |                    |                   |    |
| HsCRP, mg/L                               | 34.05±6.38         | 30.83±7.96        | 0.056|
| WBC counts, 10<sup>9</sup>/L               | 12.34±4.30         | 11.42±3.11        | 0.57|
| Neutrophil granulocyte percentage, %      | 79.89±8.51         | 83.06±6.31        | 0.33|
| Absolute neutrophil count, 10<sup>9</sup>/L | 10.03±4.09         | 9.54±2.84         | 0.74|
| Monocyte, 10<sup>9</sup>/L                | 0.54±0.14          | 0.47±0.13         | 0.54|
| Neutrophils/lymphocytes                    | 11.26±3.65         | 9.46±1.68         | 0.78|
| Random blood sugar, mmol/L                | 9.27±2.75          | 7.26±1.70         | 0.053|

<sup>1</sup> Reperfusion time (min) = duration of chest pain to the hospital (h) *60 + after admission to coronary surgery time (min);  
<sup>2</sup> preoperative oral statin drugs including 20-40 mg atorvastatin or 10-20 mh rosuvastatin;  
PCI, percutaneous coronary intervention; HsCRP, hypersensitive c-reactive protein; WBC, white blood cell.

Figure 1  Intracoronary thrombosis in percutaneous coronary intervention (PCI) (arrow).
**Table 2** Postprocedural clinical statistics of ST-segment elevation myocardial infarction (STEMI) patients.

|                          | Clopidogrel (n=20) | Ticagrelor (n=20) | P    |
|--------------------------|---------------------|--------------------|------|
| Killip ≥ grade II        | 6 (30%)             | 7 (35%)            | 0.73 |
| Ejection fraction        | 48.54±7.81          | 53.27±6.0          | 0.12 |
| **Culprit vessel**       |                     |                    |      |
| Left anterior descending coronary artery | 7 (35%) | 9 (45%) | 0.51 |
| Left circumflex          | 6 (30%)             | 5 (25%)            | 0.72 |
| Right coronary artery (RCA) | 7 (35%)       | 6 (30%)            | 0.73 |
| Intraprocedural application of temporary pacemaker | 6 (30%) | 4 (20%) | 0.46 |
| Intraprocedural application of intra-aortic ballon pump | 4 (20%) | 3 (15%) | 0.67 |
| Total triglyceride, mmol/L | 4.38±0.99        | 4.45±0.73          | 0.86 |
| High density lipoprotein, mmol/L | 1.55±0.51   | 1.46±0.63          | 0.71 |
| Low density lipoprotein, mmol/L | 1.09±0.18     | 1.05±0.23          | 0.68 |
| **Preprocedural cardiac enzyme** |                   |                    |      |
| Creatine kinase, U/L     | 303.5±10.8          | 294.36±16.37       | 0.39 |
| CK isoenzyme, U/L        | 60.6±11.4           | 55.72±15.40        | 0.13 |
| Preprocedural cardiac troponin, ng/ml | 8.58±19.21 | 6.87±4.95 | 0.16 |
| **Postprocedural blood** |                      |                    |      |
| Hypersensitive C-reactive protein | 52.49±11.53 | 37.83±10.25       | 0.11 |
| White blood cell (WBC) counts*10⁶/L | 12.7±3.76     | 10.66±1.53        | 0.12 |
| Neutrophil granulocyte percentage, % | 82.91±7.17 | 81.83±5.94 | 0.7  |
| Absolute neutrophil count *10⁶/L | 10.87±3.08 | 8.84±1.58 | 0.065 |
| Monocyte number *10⁶/L   | 0.73±0.21          | 0.87±0.69          | 0.53 |
| Neutrophils/lymphocytes  | 10.20±2.67         | 8.76±1.25          | 0.64 |
| **Postprocedural cardiac enzyme** |                   |                    |      |
| CKmax U/L                | 3204.8±251.06      | 2939.32±157.6      | 0.64 |
| CK-MBmax U/L             | 212.73±15.13       | 309.43±21.33       | 0.22 |
| Before discharge blood C-reactive protein | 7.83±9.79     | 4.48±2.50 | 0.28 |

**Expression of IL-17 and MPO detected by immunohistochemistry and Western blot analysis**

The results of immunohistochemistry are displayed in Figure 2. IL-17 and MPO were mainly detected in the plasma of inflammatory cells (eosinophils, plasma cells, and neutrophils). The expression of IL-17 and MPO in the clopidogrel group was significantly higher than that in the ticagrelor group. The APSAPs of IL-17 and MPO in the clopidogrel group were much higher (IL-17, 10.99 ± 3.20; MPO, 8.21 ± 1.71) than those in the ticagrelor group (IL-17, 4.36 ± 1.30; MPO, 4.31 ± 1.16) (P < 0.05).

**Evaluation of PCI postprocedural coronary blood flow by CTFC**

The coronary blood flow after PCI procedure was evaluated to 30 frames/s CTFC (normal). The results showed that CTFC was reduced to 23.55 ± 3.71 and 26.86 ± 1.69 in the ticagrelor and clopidogrel group, respectively. There was a significant difference between the two groups (P < 0.05).

**Following up**

We conducted regular and rigorous follow-up visits to both groups of patients, and the outcome was significantly better in Ticagrelor group than that in the clopidogrel group, regardless of the symptoms and related auxiliary examinations.
Figure 2 Detection of interleukin 17 (IL-17) and myeloperoxidase (MPO) expression in thrombus by immunohistochemistry in the ticagrelor and clopidogrel groups (200 X). APSAP: average positive staining area percentage. n = 20 for each group, *P < 0.05 between two groups using Student’s t-test.

Similarly, Western blot analysis also showed that the expression of IL-17 and MPO in the clopidogrel group (IL-17, 0.71 ± 0.036; MPO, 0.50 ± 0.07) was significantly higher than that in the ticagrelor group (IL-17, 0.50 ± 0.040; MPO, 0.38 ± 0.06) (*P < 0.05) (Figure 3).

DISCUSSION

Inflammation plays a significant role in STEMI. The present study proved that ticagrelor was more effective in exerting anti-inflammatory effect and improving blood flow than clopidogrel. The ticagrelor group showed significantly lower IL-17 and MPO expression in thrombus, as well as significantly lower CTFC than the clopidogrel group. Ticagrelor exerts anti-inflammatory effects during thrombus formation (25). The stronger antiplatelet effect of ticagrelor reduces platelet-leukocyte aggregate formation as well as inflammation (25).

IL-17 is a specific cytokine generated by the helper T lymphocytes, Th17.

Previous studies have shown that the Th17 cells positively contributed to auto-immune disorders and inflammation via production of proinflammatory IL-17 (26). Zhao et al. reported that Th17 activation existed in unstable angina and acute myocardial infarction, which might aggravate systemic and plaque local inflammatory responses and promote plaque rupture, thereby further inducing unstable angina and acute myocardial infarction (27). Other scholars report that the balance of Th17/regulatory T cells (Treg) may be critical in the pathogenesis of plaque destabilization and onset of unstable angina and acute myocardial infarction (28, 29). In addition, Th17 cells and IL-17 expression were significantly increased, while Treg cells were markedly decreased in patients with ACS (30). IL-17 was found to mediate tissue infiltration and destruction by inducing the expression of chemokines, matrix metalloproteinases, and proinflammatory cytokines (31). The present study showed that ticagrelor significantly inhibited the expression of IL-17 compared to clopidogrel, which indicated that the ticagrelor was more effective in exerting anti-inflammatory effect in ACS.

MPO is a vascular inflammatory marker released to the blood by polymorphonuclear neutrophils (32). It has been reported to promote plaque formation through the production of free radicals and activation of platelets (33). Research
has found that MPO deficient individuals have lower risk of CVD (34). Contemporary studies indicate that MPO is a novel predictive factor of adverse cardiac events in patients with ACS, especially for those with a lower level of troponin I (35, 36). High levels of inflammation in the thrombus of STEMI patients is closely related to incomplete ST-segment fall-back, worsened myocardial reperfusion, and higher ventricular remodelling risk (37). In the present study, the MPO level was significantly higher in the clopidogrel group than that in the ticagrelor group. MPO is released to the blood by activated neutrophil granulocytes and macrophages, which can oxidize low-density lipoprotein and induce red blood cell aggregation, resulting in arterial erythrocyte-rich thrombus (35). Therefore, we assumed that ticagrelor was more effective than clopidogrel in preventing vascular inflammation.

The present study confirmed the anti-inflammatory effects of clopidogrel. Clopidogrel might exert anti-inflammatory effects through the following mechanisms: first, by inhibiting the expression of P-selectin, CD40L, and tissue factors (38); second, by protecting the expression of endothelial nitric oxide synthase, which is restrained in the state of inflammation (39); third, by reducing CD3+ cells and the activity of key transcription factors in inflammation to achieve anti-inflammatory effects (40); finally, by inhibiting P2Y12 and inflammatory cytokines to release in neutrophils, lymphocytes, and macrophages (41). However, clopidogrel requires metabolism by the liver enzymes for its proper functioning, and it is affected by gene polymorphism, which limits its bioavailability (42). Ticagrelor is a novel oral antiplatelet drug that can reversibly bind to P2Y12 receptor. Notably, it does not require metabolism by the liver enzymes and is not affected by gene polymorphism (42). Therefore, for patients with no or low response to clopidogrel, ticagrelor can help prevent the occurrence of ischemic events better (43). The present study confirmed that compared with clopidogrel, ticagrelor decreased IL-17 and MPO levels in the thrombus, which indicated that ticagrelor can more potently inhibit inflammation to affect thrombogenesis by inhibiting P2Y12 receptors in the neutrophils, lymphocytes, and macrophages.

Our results were in accordance with some recent studies. Li et al. (44) compared the influence of ticagrelor and clopidogrel on inflammatory biomarkers and vascular endothelial function for patients receiving emergency PCI and demonstrated that ticagrelor could inhibit inflammation and improve vascular endothelial cell function to a greater extent than clopidogrel. Additionally, Park et al. (45) have revealed that in patients with STEMI treated by primary PCI, a 180 mg loading dose of ticagrelor is more effective in reducing microvascular injury than a 600 mg loading dose of clopidogrel. A more recent study reported that compared to clopidogrel loading, ticagrelor loading before primary PCI was not associated with reduced myocardial infarct size during the first 48 hours (46), which was not in contradiction with our findings.

Evidence has shown that ticagrelor treatment significantly increased the concentration of adenosine, which can induce ischemic preconditioning in patients (47). Li et al. (48) also suggested that ticagrelor increased adenosine and cyclic adenosine monophosphate plasma concentrations compared with clopidogrel in patients with ACS. Adenosine-enhanced ischemic preconditioning plays an important role in the prevention of sudden cardiac death, reduction of myocardial infarction area, and inhibition of tumour cell growth (47). A recent meta-analysis performed by D’Ascenzo et al. (49) showed that ischemic preconditioning reduced the incidence of PMI following PCI. Preconditioning has been considered to stabilize vulnerable plaques via inhibition of platelet aggregation and thrombogenesis (50). Therefore, the anti-thrombosis effect of ticagrelor might be associated with ischemic preconditioning. However, more clinical data are necessary to clearly explain the association between them.

Inflammatory reaction in STEMI can attenuate the effect of PCI. Inflammatory cell infiltration promotes the formation and progression of thrombus (51, 52). Activated neutrophils and monocytes can change the structural and functional characteristics of red blood cells, increase red blood cell aggregation, and increase the activity of tissue factor expression, which results in thrombus formation and affects coronary blood flow (41). Previous studies have confirmed that more MPO-positive cells (neutrophils and macrophages) in the thrombus are pumped out from the arteries during PCI in patients with acute myocardial infarction, which is related to the worsening of postprocedural myocardial blood flow (53). Animal experiments and clinical studies have found that adenosine can reduce myocardial infarction area...
and improve left ventricular function and coronary blood flow (54). Ticagrelor not only inhibits adenosine deaminase, but also increases the concentration of adenosine (55) by inducing human red blood cells to release ATP, which is broken into adenosine. Reduction in the mortality of patients with STEMI might be due to the anti-inflammatory effects of ticagrelor.

However, the small sample size of this study, which is a major limitation, should be taken into account. Therefore, further study with large sample size is needed to confirm our results.

In conclusion, the results of this study primarily indicate that preprocedural administration of rapid and high-loading dose of ticagrelor (180 mg) may significantly decrease the level of inflammatory cytokines in infarction-related artery thrombosis, when compared with clopidogrel therapy (loading dose, 600 mg). In addition, it may explain a part of the reduction in risk seen in Platelet Inhibition and Patient Outcomes.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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