Original Paper

Comparison of the Effects of Ticagrelor and Clopidogrel on Inflammatory Factors, Vascular Endothelium Functions and Short-Term Prognosis in Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Emergency Percutaneous Coronary Intervention: a Pilot Study

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Key Words

Ticagrelor • Acute STEMI • Urgent PCI • Hs-CRP • IL-6 • ESM-1

Abstract

Background/Aims: Acute ST-segment elevation of myocardial infarction (STEMI) is the most severe type of acute coronary syndrome (ACS). Particular attention has been focused on studying the pathogenesis of STEMI, and how to prevent thrombosis, reduce inflammatory reaction, stabilize plaques and improve vascular endothelial functions to preserve the survived myocardium. This study aimed to compare the anti-inflammatory endothelium-protective effects, clinical prognosis, and relevant bleeding risks of ticagrelor versus clopidogrel in patients with STEMI who underwent urgent percutaneous coronary intervention (PCI) and provide certain experimental evidence and a theoretical basis for the selection of safe and effective drugs and their proper dosage, thereby further guiding clinical medication. **Methods:** We sequentially enrolled 193 patients (104 males and 89 females) admitted to hospital due to acute STEMI. These patients underwent urgent PCI between December 2013 and May 2015 and met the inclusion criteria. They were assigned (1:1) into two groups according to different treatments, 97 patients in the ticagrelor group (treatment group), and 96 patients

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in the clopidogrel group (control group). Levels of hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), and endothelial cell-specific molecule 1 (ESM-1) taken at admission and 24 h, 4 days, and 7 days after administration, as well as the correlation between the levels of IL-6, hs-CRP, and ESM-1, were determined in the two groups. At the same time, the effects of treatment with ticagrelor and clopidogrel on the efficacy endpoint events (ischemic and safety) were explored. **Results:** No statistically significant difference was found in the levels of hs-CRP, IL-6, or ESM-1 at admission between the two groups ($P > 0.05$); Their levels were significantly elevated 24 h after administration, with statistical differences between two groups ($P < 0.05$). Furthermore, a downward trend with statistically significant differences was found on Day 4 and Day 7 ($P < 0.05$); ESM-1 levels increased along with increases of hs-CRP and IL-6 levels, indicating ESM-1 was positively correlated with hs-CRP ($r = 0.523$, $P < 0.001$) and IL-6 ($r = 0.431$, $P < 0.001$); and the occurrence rates of ischemic endpoint events at 30 days were lower in the treatment group than in the control group. The occurrence of safety endpoint events was higher than in the control group; however, no statistically significant difference was found ($P > 0.05$). **Conclusions:** Compared with clopidogrel, ticagrelor appears to rapidly reduce the prevalence of inflammatory reactions and stabilize the functions of vascular endothelium to improve the stability of atherosclerotic plaque and decrease the occurrence rate of thrombosis as well as ischemic outcome events without any obvious increase in the risk of bleeding in patients with acute STEMI receiving urgent PCI. This renders it a potential drug for clinical practice. At the same time, measurement of ESM-1, a new biological marker for vascular endothelial function disorder, could possibly become a simple, effective, and practical new method for clinical evaluation of risk stratification of patients with acute STEMI at admission.

Introduction

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As the most severe type of acute coronary syndrome (ACS), acute ST-segment elevation myocardial infarction (STEMI) is characterized by acute onset, poor prognosis, and high mortality [1]. It is caused by coronary artery endothelial injury, inflammatory rupture, and unstable plaque, which can progress to thrombosis, leading to acute occlusion of infarction related artery (IRA) and then myocardial necrosis. At present, myocardial ischemia-reperfusion, through reopening the myocardial infarction related arteries by percutaneous coronary intervention (PCI) as early as possible, has become one of the major procedures in the clinical treatment of STEMI [2, 3]. At the same time, particular attention has been focused on studying the pathogenesis of STEMI and how to prevent thrombosis, reduce inflammatory reactions, stabilize plaques, and improve vascular endothelial functions to preserve the surviving myocardium.

Inflammatory factors, including hypersensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), are involved in the vascular inflammatory reaction and development of coronary atherosclerosis [4]. As an extensively recognized indicator of inflammation, hs-CRP serves as an independent predictive factor for ACS and is important for prediction of the stability of coronary plaques, severity of vascular disorders, and occurrence rates of cardiovascular events in coronary heart disease [5, 6]. IL-6 is a pro-inflammatory factor that has also been shown to provide early prediction of underlying diseases and serious complications in patients with acute myocardial infarction, where their onset risk was positively correlated with serum IL-6 levels [7, 8]. The occurrence of inflammatory reaction leads to vascular endothelial function disorder. Endothelial cell-specific molecule 1 (ESM-1), also known as endocan, is one endothelial cell molecule that has been shown to be a potential new biological marker for vascular endothelial function disorder [9, 10]. An increase of serum ESM-1 levels was found in ACS patients, implying that ESM-1 might be a new biological marker for predicting the pathophysiological changes in vascular endothelium [11]. In addition, it has been confirmed that decreased ESM-1 levels could reduce the activation of endothelial cells, thus delaying the progress of atherosclerosis [12].

Both ticagrelor and clopidogrel are P2Y₁₂ receptor antagonists. The P2Y₁₂ receptor belongs to rhodopsin's G protein-coupled receptor family and is mainly distributed on the surface of platelet membrane. When its ligand binds to the membrane, phosphatidylinositol 3-kinase is activated, followed by activation of serine/threonine-protein kinase B, thereby exposing and cross-linking platelet glycoprotein receptors and the active site of fibrinogen and resulting in platelet aggregation and thrombus formation. Due to inadequate knowledge about ticagrelor (in comparison with clopidogrel) and its possible side effects, it has not been sufficiently used in clinical practice to date. However, ticagrelor has been shown to have some effect on reducing vascular inflammatory reactions and stabilizing endothelial function while antagonizing platelets [13-15]. In this study, we research the effects of ticagrelor and clopidogrel on inflammation and endothelial function (hs-CRP, IL-6, and ESM-1), clinical prognosis with this treatment, and relevant bleeding risks, providing certain experimental evidence and a theoretical basis for the selection of safe and effective P2Y₁₂ receptor antagonists and proper dosage, further facilitating treatment of patients with acute STEMI who undergo urgent PCI.

Materials and Methods

Clinical material

This work was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University, China. We sequentially enrolled 193 patients who were admitted to the Affiliated Hospital of Jiangnan University (Jiangsu, China) between December 2013 and May 2015 for acute STEMI. They accepted the procedure of urgent PCI and met the inclusion criteria. There were 104 males and 89 females aged 30±70 (54.82±11.09) years. After obtaining written informed consent, the patients were numbered randomly and sequentially according to their time of admission, and the random number table was looked up followed by random number sorting. The patients were divided (1:1 ratio) into two groups according to the administration of ticagrelor (loading dose of 180 mg, maintenance dose of 90 mg once, twice a day) or clopidogrel (loading dose of 600 mg, maintenance dose of 75 mg once, once a day) during the therapy, with 97 patients in the ticagrelor group (treatment group) and 96 in the clopidogrel group (control group). All of the enrolled patients signed the informed consent form and were followed up by telephone for 30 days after discharge. All the cases met the definition of acute myocardial infarction of the Third Global Seminar of ESC/ACCF/AHA/WHF and the Diagnostic Criteria of Acute Myocardial Infarction stipulated by the Chinese Society of Cardiology (2010) [16, 17]. Exclusion criteria were i) patients who would have serious adverse reactions to ticagrelor or be resistant to clopidogrel; ii) patients with a history of myocardial infarction or other heart diseases and/or severe heart failure (NYHA III or IV); iii) patients who had serious hepatic or renal function disorder; iv) patients who had a history of PCI or coronary artery bypass grafting (CABG) or had accepted other types of surgeries or been injured recently; v) patients with concomitant endocrine diseases such as diabetes, immune system diseases such as acute or chronic infections, digestive tract infections, hematological diseases, malignant tumors, and rheumatic disease of connective tissues; vi) patients with serious and uncontrolled hypertension, cerebrovascular diseases, or peripheral vascular diseases; and vii) patients who had any conditions deemed inappropriate by investigators for inclusion in the study.

Baseline measurements

The baseline measurements of patients included gender, age, body mass index (BMI), risk factors for cardiological disease (smoking, hypertension, family medical history of coronary heart disease, levels of total cholesterol, low-density lipoprotein [LDL] levels, high-density lipoprotein [HDL] level, and triglyceride levels), medications taken during the study (administration of low molecular-weight heparin, IIb/IIIa glycoprotein inhibitors, β-receptor inhibitor, ACEI, statins, CCB, nitrates, PPIs, H2RA), platelet counts, levels of glutamic oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), creatinine, urea nitrogen, blood glucose under stress, and ejection fraction value (EF value).

Measurement of hypersensitive C-reactive protein (hs-CRP)

Venous blood (5 ml) was drawn from the elbow of each subject at admission. After administration of drugs, 5 ml of fasting venous blood was again drawn from the same site on the patients at 24 h and in the mornings on Days 4 and 7. The supernatant of samples was collected for analysis by BN II automatic analyzer for protein (Siemens AG, Munich, Germany). The levels of hs-CRP in the supernatant were determined by chemiluminescence with the detection reagent of hs-CRP.

Measurement of interleukin-6 (IL-6)

Venous blood (5 ml) was drawn from the elbow of each subject at admission. After administration of drugs, 5 ml of fasting venous blood was again drawn from the same site on the patients at 24 h and in the mornings on Days 4 and 7. With no procedures for anticoagulation required, the samples were immediately placed at 4°C to coagulate for 1 h. Samples were centrifuged at 3000 rpm/min for 15 min at 4°C, and the serum was drawn into EP tubes and stored at –80°C until measurement. The expression levels of IL-6 were measured by ELISA according to manufacturer's instructions (RB Co., Ltd., USA).

Endothelial cell-specific molecule 1 (ESM-1)

Venous blood (5 ml) was drawn from the elbow of each subject at admission. After administration of drugs, 5 ml of fasting venous blood was again drawn from the same site on the patients at 24 h and in the mornings on Days 4 and 7. Samples were put in a supine position for ≥20 min without any procedures for anticoagulation and then immediately placed at 4°C to coagulate for 1 h. Samples were centrifuged at 3000 rpm/min for 15 min at 4°C, and the serum was drawn into EP tubes and stored at –80°C until measurement. The expression levels of ESM-1 were measured by ELISA according to the manufacturer's protocol (Shanghai Enzyme-Linked Biotechnology Co., Ltd., Shanghai, China).

Observation of primary efficacy endpoint

A 30-day follow-up was performed for the patients in the two groups, and the items for statistical analysis included occurrence rates of ischemic endpoint events, including cardiac death, acute myocardial infarction, symptoms with the urgent need for coronary revascularization, and cerebral stroke and occurrence rates of bleeding events (e.g., identifying the occurrence rate of major bleeding events during hospitalization and in the 30 days after surgery according to Platelet Inhibition and Patient Outcomes [PLATO]). The bleeding events tracked and listed included the following: i) major bleeding events (life-threatening or lethal) such as fatal intracranial bleeding, hypotension requiring a pressure-increasing agent or surgery, pericardial bleeding with tamponade, hypovolemic shock, or clinically obvious or significant bleeding with hemoglobin decreased by more than 5 g/dL, and bleeding requiring transfusion of 4 or more units of blood (whole blood or bag-packaged red blood cells); ii) other major bleeding such as those causing significant loss of function (e.g., intraocular bleeding with permanent blindness); clinically obvious or significant bleeding with hemoglobin decreased by 3–5 g/dL; and bleeding requiring transfusion of 2–3 units of blood; iii) secondary bleeding, defined as non-serious bleeding requiring medical intervention for hemostasis or treatment; and iv) slight bleeding, meaning other bleeding with no requirement for medical intervention (e.g., bruises, gingival bleeding, and bleeding at the injection site) [18].

Statistical method

Data analysis was performed using SPSS 22.0 statistical software (IBM, Armonk, NY, USA). Quantitative data were presented as the mean ± standard deviation ($\bar{x} \pm s$). A normality test was conducted. If the data were consistent with normal distribution, an independent-sample t-test was applied for analysis of the differences between the two groups; otherwise, the Mann–Whitney rank-sum test was utilized. Enumeration data were presented as cases/percentage (n/%), tested by Chi-square (χ^2) test or Fisher exact probability test. For correlation analysis among variables, if the variable met bivariate normal distribution, Pearson product-moment correlation analysis was performed; otherwise, Spearman rank correlation analysis was applied. P-values less than 0.05 were considered as statistically significant.

Table 1. Comparison of baseline measurements in the two groups. Note: No statistically significant differences were found in baseline measurements ($P>0.05$). BMI, body mass index. TC, total cholesterol. LDL, low-density lipoprotein. TG, triglyceride. ACEI, angiotensin-converting-enzyme inhibitor. CCB, calcium channel blocker. PPIs, proton pump inhibitors. H2RA, H₂ antagonists. GOT, glutamic oxaloacetic transaminase. GPT, glutamic-pyruvic transaminase. cTnI, troponin I. BNP, brain natriuretic peptide. EF, ejection fraction

Variables	Treatment group (N=97)	Control group (N=96)	P value
Gender (male/female)	51/46	54/42	0.609
Age (years)	55.90±11.39	53.73±10.80	0.176
BMI (kg/m ²)	25.01±2.57	24.34±2.47	0.066
Cardiovascular risk factors, n (%)			
Smoking	49 (50.5)	53 (55.2)	0.514
Intake of alcohol	64 (66.0)	61 (63.5)	0.723
Hypertension	37 (38.1)	42 (43.8)	0.428
Family medical history of coronary heart disease	9 (9.3)	13 (13.5)	0.351
TC (mmol/L)	4.68±1.01	4.59±0.85	0.512
LDL-C (mmol/L)	3.16±0.57	3.19±0.49	0.650
TG (mmol/L)	1.32±0.50	1.39±0.46	0.343
The medications during the study, n (%)			
Low molecular weight heparin	97 (100.0)	96 (100.0)	-
Iib/IIIa glycoprotein inhibitors	41 (42.3)	37 (38.5)	0.598
β receptor blocker	52 (53.6)	56 (58.3)	0.509
ACEI	56 (57.7)	52 (54.2)	0.618
ARB	18 (18.6)	16 (16.7)	0.730
Statins	97 (100.0)	96 (100.0)	-
CCB	24 (24.7)	23 (24.0)	0.899
Nitrates	59 (60.8)	57 (59.4)	0.837
PPIs	50 (51.5)	53 (55.2)	0.610
H2RA	23 (23.7)	26 (27.1)	0.590
Blood markers, n (%)			
GOT (u/L)	39.01±6.87	40.04±6.85	0.298
GPT (u/L)	34.25±5.61	35.36±5.79	0.175
Creatinine (umol/L)	87.52±16.87	91.81±17.89	0.088
Urea nitrogen (mmol/L)	6.85±2.42	7.26±2.23	0.230
Blood glucose under stress (mmol/L)	7.59±2.81	8.26±2.50	0.080
cTnI (ng/mL)	3.20±1.24	3.46±1.33	0.174
BNP (pg/mL)	210.56±36.52	220.28±41.88	0.087
EF	0.50±0.06	0.51±0.08	0.188

Results

Comparison of baseline material in the groups

No statistically significant differences ($P>0.05$) between the groups were found for gender; age; BMI; risk factors for cardiological events (smoking, intake of alcohol, hypertension, family medical history of coronary heart disease, levels of total cholesterol, LDL levels, and triglyceride levels); medications taken during the study (including administration of low molecular-weight heparin, IIb/IIIa glycoprotein inhibitors, β -receptor inhibitor, ACEI, ARB, statins, CCB, nitrates, PPIs, H2RA); and levels of GOT, GPT, creatinine, urea nitrogen, blood glucose under stress, cTnI, BNP, and EF ($P>0.05$, see Table 1)

Comparison of the levels of hs-CRP, IL-6, and ESM-1 between the groups

No statistically significant difference was found in hs-CRP, IL-6, and ESM-1 levels at admission between the two groups ($P>0.05$). Their levels were significantly elevated 24 h after administration, with statistical differences between the groups ($P<0.05$). Furthermore, on Days 4 and 7, we found a downward trend, with statistically significant differences between the groups ($P<0.05$, see Table 2 and Fig. 1-3)

Correlation of ESM-1 with hs-CRP and IL-6 at admission

To investigate the correlation of ESM-1 with hs-CRP and IL-6 at admission, a bivariate analysis was performed. ESM-1 levels increased with increases of hs-CRP and IL-6 levels, indicating that ESM-1 is positively correlated with hs-CRP ($r=0.523$, $P<0.001$) and IL-6 ($r=0.431$, $P<0.001$,) (see Table 3 and Fig. 4-5).

Comparison of major efficacy endpoint events between the groups

The occurrence rates of ischemic endpoint events (including cardiac death, non-fatal myocardial infarction, symptoms with an urgent need for coronary revascularization, and cerebral stroke) within 30 days were lower in the treatment

Fig. 1. Comparison of serum levels of hs-CRP in patients in the two groups at different time points. *, $P<0.05$; hs-CRP, high-sensitivity C-reactive protein.

Fig. 2. Comparison of serum levels of IL-6 in patients in the two groups at different time points. *, $P<0.05$; IL-6, interleukin-6.

Fig. 3. Comparison of serum levels of ESM-1 in patients in the two groups at different time points. *, $P<0.05$; ESM-1, endothelial cell-specific molecule 1.

Table 2. Comparison of levels of hs-CRP, IL-6, and ESM-1 in the two groups. hs-CRP, high-sensitivity C-reactive protein. IL-6, interleukin-6. ESM-1, endothelial cell-specific molecule 1

Variables	Treatment group (N=97)	Control group (N=96)	P value
hs-CRP (mg/L)			
At admission	7.83±2.81	7.90±2.75	0.867
24h after administration of drugs	26.07±5.21	27.80±6.75	0.048
4th day of administration of drugs	12.46±3.94	14.81±5.54	0.001
7th day of administration of drugs	6.15±1.63	7.02±2.32	0.003
IL-6 (pg/mL)			
At admission	14.17±1.62	14.34±1.41	0.422
24h after administration of drugs	28.90±4.34	30.11±4.17	0.049
4th day of administration of drugs	24.84±4.05	26.01±3.88	0.041
7th day of administration of drugs	12.76±1.76	13.48±1.49	0.003
ESM-1 (ng/mL)			
At admission	1.12±0.15	1.11±0.18	0.699
24h after administration of drugs	1.19±0.18	1.26±0.19	0.021
4th day of administration of drugs	1.12±0.17	1.19±0.18	0.012
7th day of administration of drugs	1.04±0.16	1.11±0.15	0.002

Table 3. Analysis of correlation between hs-CRP and IL-6 with ESM-1. hs-CRP, high-sensitivity C-reactive protein. IL-6, interleukin-6. ESM-1, endothelial cell-specific molecule 1

Variables		hs-CRP	IL-6
ESM-1	r value	0.523	0.431
	P value	<0.001	<0.001

group than in the control group, and the occurrence rates of safety endpoint events (bleedings) were higher in the treatment group than in the control group. However, the differences were not statistically significant ($P>0.05$). See Table 4.

Discussion

Acute thrombosis within coronary arteries caused by rupture of atherosclerotic plaque is the main cause of acute STEMI where the pathophysiological changes in platelet inflammatory factors and vascular endothelium are involved. The inflammatory factors, such as hs-CRP, TNF- α , matrix metalloproteinases (MMPs), IL-6, IL-8, IL-37, CD40 and its ligand, vascular cell adhesion molecule 1 (VCAM-1), and selectins, are involved in the vascular inflammatory reaction and the pathogenesis and development of coronary atherosclerosis [4]. The occurrence of inflammatory reaction leads to vascular endothelial function disorder and thinning and rupture of the fibrous cap of atheromatous plaque while also activating extrinsic coagulation pathways, eventually resulting in platelet aggregation and formation of thrombi [19].

Vascular endothelium, a monolayer of cells covering

Fig. 4. Scatter diagram of the correlation between hs-CRP and ESM-1 levels. hs-CRP, high-sensitivity C-reactive protein; ESM-1, endothelial cell-specific molecule 1.

Fig. 5. Scatter diagram of the correlation between IL-6 and ESM-1 levels. IL-6, interleukin-6; ESM-1, endothelial cell-specific molecule 1.

Table 4. Comparison of efficacy endpoint events between the two groups at 30 days

Variables	Treatment group (N=97)	Control group (N=96)	P value
Ischemic endpoint events, n (%)	3 (3.1)	7 (7.3)	0.322
Cardiac death	1 (1.0)	1 (1.0)	0.999
Non-fatal myocardial infarction	1 (1.0)	4 (4.2)	0.211
Urgent coronary revascularization	0 (0.0)	0 (0.0)	-
Cerebral stroke	1 (1.0)	2 (2.1)	0.621
Safety endpoint events, n (%)	7 (7.2)	5 (5.2)	0.563
Major bleeding events	0 (0.0)	0 (0.0)	-
Other major bleeding events	0 (0.0)	0 (0.0)	-
Secondary bleeding events	4 (4.1)	3 (3.1)	0.999
Slight bleeding events	3 (3.1)	2 (2.1)	0.999
Total adverse events, n (%)	10 (10.3)	12 (12.5)	0.632

the intima of a vessel, plays an important role in both physiological and pathological processes. Physiologically, the vascular endothelium exerts multiple important effects, including regulating the bloodstream, maintaining the balance of blood fibrinolysis and coagulation systems, inhibiting proliferation of vascular endothelium, chemotactic adhesion of inflammatory cells, and platelet aggregation [20]. Under pathological conditions such as vascular endothelial function disorder caused by endothelial injury, the above-mentioned physiological equilibrium is disturbed, resulting in inflammatory cell chemotaxis, increased activity of inflammatory factors, white platelet aggregation, and eventual thrombosis [21]. Vascular endothelial function disorder has been shown to be one of the early factors affecting atherosclerosis, and thus, early identification would be beneficial for evaluation and prediction of cardiovascular events, particularly acute myocardial infarction [22].

Ticagrelor, a new P2Y₁₂ receptor antagonist, was launched late in the China market. Compared to clopidogrel, ticagrelor could, without metabolic activation, take effect immediately after oral administration with a median peak of about 1.5 h, binding to the P2Y₁₂ receptor reversibly and resulting in a rapid recovery of platelets after drug withdrawal [23]. Aside from platelet membranes, the P2Y₁₂ receptor is also expressed on the surface of inflammatory cells. It has been reported that the chemotaxis of inflammatory cells, including macrophages, was compromised in mice with a P2Y₁₂ receptor defect [24]. Moreover, multiple studies have demonstrated that a P2Y₁₂ receptor antagonist could affect the migration of inflammatory cells through inhibition of P2Y₁₂ receptors on the surface of inflammatory cells, such as microglial cells, neutrophils, dendritic cells, and mononuclear macrophages [25, 26], indicating that ticagrelor may produce other pharmacological effects in a similar manner.

As an extensively recognized indicator of inflammation with high sensitivity and specificity, hs-CRP interacts with vascular endothelial cells and other cells to accelerate the process of vascular inflammatory reactions, causing plaques inside the coronary artery to rupture and leading to a series of pathological and physiological processes such as leukocyte adhesion, platelet aggregation, and newly developed thrombosis. As a result, hs-CRP has served as an independent predictive factor for ACS and is of important significance in prediction of the stability of coronary plaques, severity of vascular disorders, and occurrence rates of cardiovascular events in coronary heart disease [5, 6]. IL-6 is a pro-inflammatory factor that could induce the liver to produce acute phase proteins and fibrinogen, further aggravating inflammation in coronary arteries and accelerating thrombus formation. Moreover, IL-6 and its signal transducer gp130 could further enhance the adhesion between white blood cells and myocardial cells by increasing the expression of adhesion molecules on myocardial cells, thereby aggravating myocardial cell injury [27, 28]. IL-6 was also shown to predict early underlying diseases and serious complications in patients with acute myocardial infarction, where their onset risk was positively correlated with serum IL-6 levels [7, 8]. In this study, we found that serum levels of hs-CRP and IL-6 in the treatment group were lower than those in the control group at 24 h, 4 days, and 7 days after administration of drugs, with statistically significant differences ($P < 0.05$). This indicates the superiority of ticagrelor to clopidogrel in inhibition of inflammation in addition to its potent anti-platelet effect. The anti-inflammatory mechanism is possibly related to the direct effect of ticagrelor on P2Y₁₂ receptors without liver metabolic activation, thereby rapidly and potently inhibiting adenosine diphosphate (ADP) mediated platelet aggregation and further suppressing the release of inflammatory factors and expansion of the inflammatory cascade reaction. In addition, ticagrelor may exert anti-inflammatory, anti-arteriosclerotic, anti-fibrotic, and heart-protective effects through increasing ADP concentration in the blood, which is consistent with a study by Jacobson et al. [29]. However, different opinions have been expressed by foreign scholars. As shown, no obvious decrease was found of inflammatory markers in the ticagrelor group compared with the clopidogrel group in patients with non-ST-segment elevation ACS [30]. Therefore, further clinical studies and experiments are needed to demonstrate whether the P2Y₁₂ receptor inhibitor ticagrelor, as compared to clopidogrel, can further reduce serum inflammatory marker (e.g., hs-CRP or IL-6) levels in patients with acute STEMI, where this

special anti-inflammatory effect would provide clinical benefit for those patients.

ESM-1 was first cloned from the cDNA library of human umbilical vein endothelial cells and reported by French scientist Lassalle in 1996 and is mainly distributed in pulmonary and renal vascular endothelial cells [31]. The molecular weight of initially secreted ESM-1 is about 50 kDa, and after transcriptional modification, its molecular weight decreases to 20 kDa. Maturely expressed ESM-1 is a highly conservative protein comprised of repetitive cysteines and one polypeptide containing 165 amino acids. It is covalently bound by a highly glycosylated mucopolysaccharide at the 137th serine binding site in the polypeptide. Multiple studies have shown that ESM-1 may be a new biological marker for vascular endothelial function disorder and play an important role in regulating cell adhesion, migration, and proliferation [9, 10]. Since ESM-1 is highly expressed in atherosclerotic plaques, it was proposed that the increased secretion of ESM-1 could increase the migration and proliferation of vascular smooth muscle cells (VSMC), thereby affecting the occurrence and development of atherosclerosis. Kose et al. [11] found an increase of serum ESM-1 levels in ACS patients, inferring that ESM-1 might be a new biological marker for predicting the pathophysiological changes in vascular endothelium. In addition, Tadzic et al. [12] confirmed that a decrease of ESM-1 levels could reduce the activation of endothelial cells, thus delaying the progress of atherosclerosis. In the present study, we found that ticagrelor and clopidogrel alleviated the effect of ESM-1 to varying degrees, and statistically significant differences were found in the ESM-1 levels in both the ticagrelor group and the clopidogrel group at 24 h, 4 days, and 7 days after administration of drugs ($P < 0.05$), indicating that P2Y₁₂ receptor antagonists could improve vascular endothelial function. Importantly, ticagrelor was superior to clopidogrel. These results indicate that the potent and unique anti-thrombotic and anti-inflammatory effects of ticagrelor may account for its role in acute STEMI.

To confirm the correlation of ESM-1 with inflammatory markers and its role in the complete pathophysiological process of acute STEMI, including the pathogenesis, development, and prognosis, a correlational analysis of ESM-1 and hs-CRP and IL-6 levels was performed. The results showed that ESM-1 levels were increased with the increase of hs-CRP and IL-6 inflammatory marker levels, suggesting ESM-1 was positively related with both hs-CRP and IL-6 ($r = 0.523$, $P < 0.001$; $r = 0.431$, $P < 0.001$). It is presumed that ESM-1, the marker of endothelial function disorder, could be involved in the pathogenesis and development of acute coronary events in coronary heart disease through a series of complicated mechanisms in which ESM-1 activated the release of inflammatory factors such as hs-CRP and IL-6, and in turn, the inflammatory factors promoted the expression of ESM-1. This has rarely been reported either here or overseas, and thus, the correlation between ESM-1 and the inflammatory markers in STEMI needs to be further studied.

The PLATO trial is a landmark study of 18,624 patients from 43 countries and 862 centers, which continues for a period of 2 years. In our country, 416 patients participated in this study. The results, including those from the invasive therapy subgroup, showed ticagrelor had more potent inhibition on platelets in ACS patients as compared to clopidogrel, which could significantly reduce the occurrence rates of cardiac death, myocardial infarction, or stroke, thereby improving the prognosis of ACS patients without increasing overall major bleedings. However, the occurrence rates of non-procedural related bleeding were increased [32]. In this study, the tendency toward the occurrence of efficacy endpoint events (ischemic endpoint events, safety endpoint events, and overall adverse events) in the two groups was similar to those in the PLATO trial; however, no statistically significant difference was found. The possible reasons for this include our study's small sample size. Significant results may be found if the sample size is enlarged. A further potential factor is the population included in our study. In the PLATO trial, ACS patients were included, whereas, in this trial, only patients with acute STEMI were enrolled. More factors may be involved in the occurrence of efficacy endpoint events, especially ischemic endpoint events, which will be further investigated and explored in the future.

Limitations of our study include the following: i) The samples collected were from the patients in the department of cardiology at a single center; therefore, the study results

may only represent inpatients at that center. ii) Due to the limited duration of the study, the sample size collected is relatively small, causing a certain deviation in the statistical results, particularly the results of efficacy endpoint events where only descending or ascending tendency remains, without a statistically significant difference. iii) The duration of follow-up is short. Only a 30-day short-term follow-up was performed without a long-term follow-up on prognosis. iv) A comparative study on the dynamic changes of relevant parameters was performed in the two groups. Although a great significance at several time points on the basis of previous studies was observed, the dynamic changes at multiple time points may be more valuable for clinical guidance. These deficiencies will be further refined and improved in the future.

Conclusion

In the treatment of patients with acute STEMI receiving urgent PCI, as compared with clopidogrel, ticagrelor could better decrease the levels of inflammatory factors, reduce the prevalence of inflammatory reactions, and stabilize vascular endothelial functions to improve the stability of atherosclerotic plaque and decrease the occurrence rate of thrombosis and ischemic outcome events without any obvious increase in the risk of bleeding. Therefore, ticagrelor should be recommended in clinical practice. Meanwhile, measurement of ESM-1, a new marker for vascular endothelial function disorder, may become a simple, effective, and practical method for clinical evaluation of the risk stratification of patients with acute STEMI at admission.

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