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IMPACT OF STATINS COMBINATION WITH DUAL ANTIPLATELET THERAPY ON ANTI-INFLAMMATORY FACTORS AND MYOCARDIAL PROTECTIVE EFFECTS IN ACUTE STEMI PATIENTS AFTER EMERGENCY PCI

Zakarya Ahmed*[1], MD, Hesong Zeng*[1], MD, PhD, Chang Xu[1], MD, PhD and NaNa Tang[1], BSN.

Department of Cardiology, Tongji Hospital, Tongji Medical College Huazhong University of Science and Technology, Wuhan, 430030, Hubei Province, P.R. China.

***Corresponding Author: Hesong Zeng, MD, PhD,**
Department of Cardiology, Tongji Hospital, Tongji Medical College Huazhong University of Science and Technology, Wuhan, 430030, Hubei Province, P.R. China.

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ABSTRACT

Background: Early reperfusion of the occluded coronary artery which cause an acute myocardial infarction extremely concerned important for the reduction of infarction size and the retrieval of ventricular function. A participation in microvascular injury, the balance between protective and harmful inflammatory factors may have roles in reperfusion injury and may affect final ventricular remodeling. **AIMS:** This Study aims to compare the anti-inflammatory effects of atorvastatin or rosuvastatin when co-administered with ticagrelor versus clopidogrel as a long-term treatment for AMI patients underwent urgent PCI. Moreover, to compare the effectiveness of NT-proBNP and left ventricular ejection fraction (LVEF) in predicting prognosis of STEMI. **Methods:** We retrospectively analyzed 490 patients who underwent urgent PCI for AMI from 2015 to 2017 in our hospital. We compared the effects of four therapeutic groups (atorvastatin/ticagrelor AT, atorvastatin/clopidogrel AC, rosuvastatin/ ticagrelor RT, and rosuvastatin/clopidogrel RC) on the related indicators of serum inflammatory factors, NT-proBNP, and left ventricular remodeling. We also compared the combined endpoint which was cardiovascular death, MI, or stroke at 12 months after PCI. **Results:** No statistically significant difference was found in the levels of HCY, MHR, NLR, NT-proBNP, LVD, LAD and LVEF at the admission time between the four groups ($P>0.05$); However, their levels most decrease was observed at group AT after 12 months ($P<0.05$). The incidence rates of ischemic endpoint events within 12months were lower in the AT group than in the other groups (3 (2.7%), 2(1.8%), 4(3.0%), and 3(2.2%) at groups AT, AC, RT, and RC) $P<0.023$. The occurrence rate of the major bleeding was similar in the groups AT, and RT (3 (2.6%), 2 (1.8%), 3 (2.2%), and 1 (0.7%) at AT, AC, RT, and RC groups, $P<0.05$, respectively. However, the differences noticed in the cardiac death, re-attack of myocardial infarction, urgent coronary revascularization, cerebral stroke, safety endpoint events, secondary bleeding events slight bleeding events were not statistically significant ($P>0.05$). **Conclusions:** Among patients receiving DAPT, rosuvastatin but not atorvastatin is associated with an increased rate of HRPR for clopidogrel, without any influence on the antiplatelet effect of ASA or ticagrelor. Therefore, cautiousness should be exerted for clopidogrel and rosuvastatin therapeutic association.

KEYWORDS: atorvastatin; rosuvastatin; ticagrelor; clopidogrel; acute myocardial infarction; homocysteine.

BACKGROUND

Developments in coronary artery revascularization techniques and the pharmacological strategies have positively affected the outcomes of coronary artery disease (CAD) patients, especially in acute coronary syndromes (ACS)[1,2], in which their benefits are excessively obtained from high-intensity statins and more effective dual antiplatelet therapy (DAPT).[3,4] AMI as the most severe types of ACS, whether caused by an inflammatory rupture process, impairment of the coronary artery endothelial cells or unstable ruptured plaque, can progress to thrombosis, which may lead to acute occlusion of the related coronary artery which may be developing to the necrosis of that part of the myocardium. Currently, a reperfusion of the myocardial ischemia, by removing or opening the culprit vessels arteries via percutaneous coronary intervention (PCI) as early as possible, has become one of the major procedures in the clinical treatment of STEMI.[5] As well, 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.

Acute MI causes a domestic and systemic inflammatory reaction, which facilitates atherosclerosis, triggers the autonomic nervous system, and contributes to left ventricular remodeling.[6,7] A study (Takehiko Washio and Kazumiki Nomoto et all) had shown a high levels of plasma homocysteine in patients with AMI might be associated to the progression of heart failure, an elevated plasma homocysteine levels seem to be a distinct predictor of further predictable risk features of heart failure.[8] Lipids and Inflammatory factors are two important markers of atherosclerosis as a chronic disease. Recently, numerous studies have shown that monocytes had a close relation with in-stent fibrin deposition, furthermore monocyte-derived tissue factor had a profound effecting stent thrombosis.[9] Principal effects of high-density lipoprotein (HDL) particles on monocytes have been confirmed, presented as progression of cholesterol efflux from macrophages, impeding the differentiation of monocytes, inhibiting inflammatory signaling and processes.[10] A study shows that M/H ratio as a novel marker of inflammation appeared to be an important predictor of certain stent thrombosis post-PCI for STEMI. Therefore, M/H ratio could be used for the prediction of stent thrombosis as a high-risk complication and in the individualization of targeted therapy.[10]

Ticagrelor is a P2Y12 antagonist, it is non-thienopyridine with a reversible effect that gives quicker, more effective, and reliable platelet inhibition than clopidogrel.[11] The Platelet Inhibition and Patient Outcomes (PLATO) is large multi-national randomized controlled trial had demonstrated that ticagrelor was related with lower incidence of cardiovascular mortality, myocardial infarction, or stroke compared with clopidogrel in patients with ACS in the combination with aspirin.[12] therefore, the use of ticagrelor is favored over clopidogrel in acute coronary syndrome (ACS), the recommendation level is IIa according to the recent ACC/AHA guidelines for ACS management.[13, 14]

High intensity statins effects which have been achieved by the contrasting results[15], such as rosuvastatin and atorvastatin, as their co-administration with clopidogrel or ticagrelor often occurs in patients with CAD also, the statins known that their efficacy could be inactivated by the CYP2C19 and CYP3A4enzymatic system, it might interact with clopidogrel activation. there are a few data which have been reported that statin can reduce the levels of myocardial injury in AMI, in addition to reduce inflammation and inhibit ventricular remodeling.[16,17] Yellon's laboratory confirmed that acute administration of Atorvastatin at the onset of reperfusion resulted in a reduction in infarct size in a mouse Langendorff model of ischemia-reperfusion. This was seen to be dependent on PI3 Kinase and AKT activation of eNOS8. Similar results were also reported in the rat in vivo experiments when Simvastatin was acutely administered during reperfusion.[18] A large trial (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) known as ARMYDA study[19] proved that the short time administration of atorvastatin before percutaneous coronary intervention (PCI) shows a significant reduction of periprocedural myocardial infarction (PMI) in statin-naïve patients. The ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes) trial also had confirmed this myocardial protective effects[20], in acute coronary syndromes (ACS) statin-naïve patients given a high-dose atorvastatin 12 hours before PCI procedure confirmed the reduction of 30-day cardiac events.[21]

During recent years, a new type of statin drugs rosuvastatin, although it has a stronger lipid-lowering effects, but only few studies investigated its inflammatory effects and left ventricular remodeling for the treatment of ST segment elevation myocardial infarction (STEMI) patients after PCI procedure. Also, there are few reports on the effect of atorvastatin whether combined with clopidogrel or ticagrelor on inflammatory factors such as Homocysteine (HCY), highly sensitive c reactive protein (hs-CRP) and prognosis in patients with unstable angina.

Therefore, our retrospective study objectives were a) to inspect whether if chronic treatment with the common dose of atorvastatin or rosuvastatin for one year in combination with a ticagrelor may bring additional beneficial effects on ischemia-induced impaired heart function after a brief period of Acute total coronary occlusion induced MI as compared to combination with a clopidogrel treatment in STEMI patients underwent Urgent primary PCI, and b) to observe whether atorvastatin or rosuvastatin combined with ticagrelor or clopidogrel can reduce the serum levels of inflammatory parameters both in coronary and in peripheral vascular system in patients with STEMI or not. Moreover, and to compare the effectiveness of NT-proBNP and left ventricular ejection fraction (LVEF) in predicting prognosis of STEMI

MATERIALS AND METHODS

Study design & Study population

In this retrospective study we analyzed the medical records of 490 Eligible patients whom underwent Urgent primary PCI management for acute ST segment elevation myocardial infarction (STEMI), the study protocol did not require informed consent and was approved by the Institutional Review Board of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, HuBei province. To make a parallel comparison of ticagrelor versus clopidogrel throughout the same study duration, we screened eligible patients from January 2015 until December 2017.

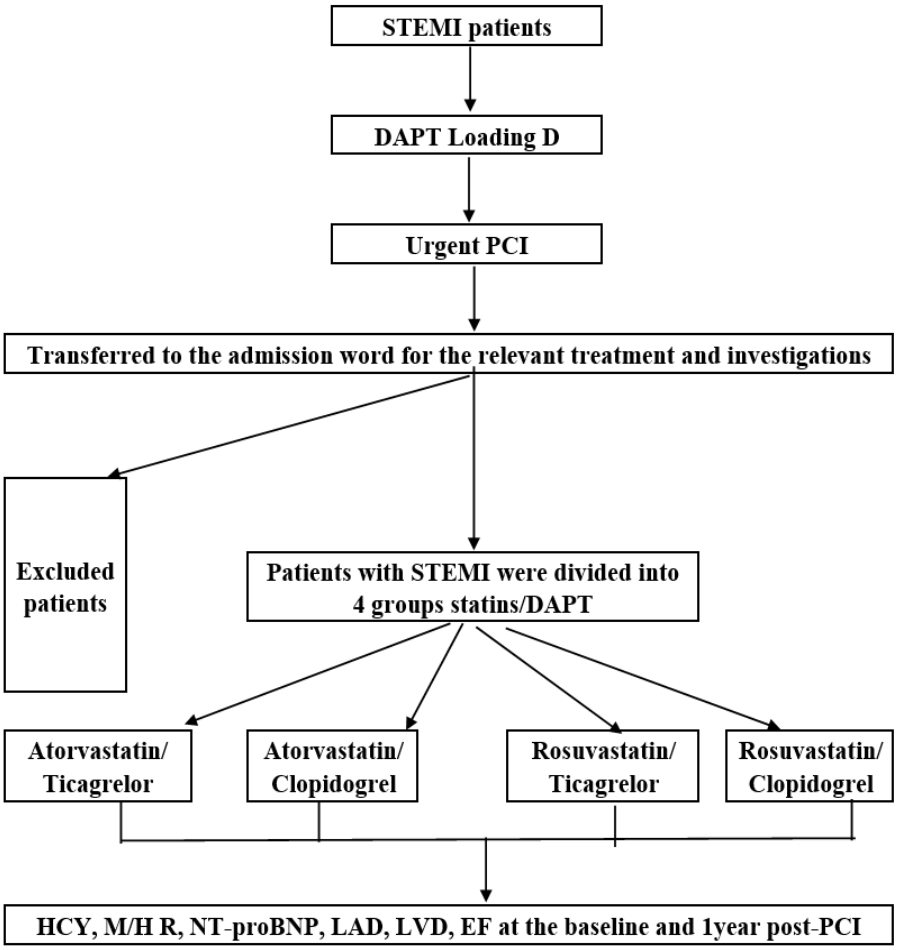

Fig.1 our study flowchart. After Urgent PCI therapy performed During the 1st 24 h from symptoms onset, subjects with successful PCI were transferred to the admission word and given the related investigations and drug management, until their condition improved, they discharged with DAPT, Statins and other related Drugs. Each included patient was recorded into one of the four assignments (atorvastatin/ticagrelor, atorvastatin/clopidogrel, rosuvastatin/ticagrelor, or rosuvastatin/ticagrelor). The Lab results were collected at baseline, and 360 days after PCI.

Ticagrelor had been listed and available in the hospital since the given dates. The following screening criteria were applied for all selected patients in this study: (1) patients with discharge diagnosis of acute ST segment elevation myocardial infarction (STEMI), and successfully received primary percutaneous coronary intervention (PPCI) according to the Guideline for the Management of STEMI[22]; (2) patients who were taking ticagrelor or clopidogrel with atorvastatin or rosuvastatin on or before discharge. Based on the drug administration during the admission time, the patients were divided into four groups: A (atorvastatin with ticagrelor n=108), B (atorvastatin with clopidogrel n=112), C (rosuvastatin with ticagrelor n=133), and D (rosuvastatin with clopidogrel n=137). The endpoint and clinical data of our study were collected and recorded from the medical chart review if patients were regularly followed up in our hospital; however, the contact with the participants or their relatives was made for patients without regular medical follow-up. But the authors collected the data in an anonymous method with no direct contact with participants or their relatives. The only exclusion criteria were: 1) predicted noncompliance to dual antiplatelet treatment for at least 6 months; 2) in-hospital death that was not caused by stent thrombosis; and 3) early withdrawal of clopidogrel or ticagrelor therapy after PCI.

Outcome measurement

In this study we retrospectively compared the changes of Homocysteine, Hs-CRP, Monocyte HDL ratio, and the N-terminal pro b-type natriuretic peptide (NT-proBNP) Improvement, in addition to heart function assessed by the left ventricular ejection fraction (LVEF), left atrium and ventricular diameter at the baseline and one year after discharging. NT-proBNP was detected by immunofluorescence, Hs-CRP was detected by enzyme linked immunosorbent assay (ELISA) both reagents were provided by Finnish Orion Corporation), HCY reagents were provided by Bio-Rad Laboratories Hercules, California, United States of America. The left ventricular ejection fraction (LVEF) was detected by GE healthcare voluson e8 color Doppler echocardiography in our hospital.

Statistical analysis

Statistical analysis was performed by SPSS Statistics Software 22.0. (SPSS Inc., Chicago, Illinois). Continuous variables were represented as mean ± SD, while categorical variables as percentage. Chi-Squared and ANOVA test were appropriately used to compare clinical and laboratory features according to the type of statin treatment. A p value < 0.05 was considered statistically significant.

RESULTS

Main demographic and clinical characteristics

We screened out a number of 490 patients who confirmed diagnosis of acute STEMI patients successfully underwent Emergency PCI, 112 (22.9%) were on atorvastatin and ticagrelor (group AT), 108 (22.0%) on atorvastatin plus clopidogrel (group AC). 133 (27.1%) on rosuvastatin plus ticagrelor (group RT), and 137 (28.0%) were on rosuvastatin plus clopidogrel (group RC). The baseline demographic and clinical characteristics parameters are displayed on (Table-1), there were no significant differences between the four groups treatment combination.

Procedural characteristics

The comparation of angiographic features were conducted among the 4 groups (Table 2). A longer length of Onset to balloon was found in group AT than the other group. There was significant difference in the relative number of disease-vessels and spreading in the location of infarction-related artery (IRA) between the groups. Significantly higher number of patients in the RT group had a notable increased proportion of coronary IRA located in left anterior descending artery (LAD) (43(38.4%), 33(30.5%), 56(42.1%), and 52(37.9%) in the four groups respectively, P<0.05. Results were confirmed after correction for baseline stent features differences, with no different in the four groups (Table 2).

Table 1: Main clinical and demographic features.

Parameters	AT	AC	RT	RC	P. Value
Age	55.27±8.83	54.18±8.65	56.38±9.56	54.64±9.07	0.248
Male sex (%)	90(80.3)	87(80.5)	106(79.7)	101(73.7)	0.485
BMI	26.61±3.31	26.62±4.27	27.30±4.01	27.05±4.20	0.452
Hypertension (%)	53(47.3)	55(50.9)	75(56.4)	69(50.3)	0.544
Active Smokers (%)	63(56.2)	61(56.4)	66(49.6)	60(43.8)	0.140
Diabetes mellitus (%)	24(21.4)	18(16.7)	29(21.8)	33(24.1)	0.564
Previous MI (%)	10(9.8)	12(11.1)	11(8.2)	14(10.2)	0.879
Previous PCI (%)	19(16.9)	9(8.3)	18(13.5)	17(12.4)	0.291
Previous CABG (%)	4(3.6)	10(9.2)	5(3.8)	10(7.3)	0.183
Killip class >1(%)	18(16.1)	10(9.2)	12(9)	15(10.9)	0.294
Multivessel CAD	31(27.7)	39(36.1)	47(35.3)	51(37.2)	0.689
ACE inhibitors (%)	97(86.6)	92(85.2)	114(85.7)	113(82.5)	0.812
ARBs (%)	7(6.3)	4(3.7)	4(3)	12(8.8)	0.160
Beta blockers (%)	90(80.4)	89(82.4)	104(78.2)	108(78.8)	0.857
Ca-antagonists (%)	10(8.9)	11(10.2)	21(15.8)	11(8)	0.174
PPIs (%)	58(51.8)	51(47.2)	78(58.6)	79(57.7)	0.251
Random Blood Sugar	6.73±2.26	6.93±.91	6.61±1.85	6.99±.47	0.554
HbA1c	6.08±.74	6.09±2.16	5.94±1.07	6.17±.29	0.685
(AST)	55.74±54.31	62.18±67.61	58.43±55.85	65.57±80.98	0.662
(ALT)	43.82±25.52	46.48±32.72	43.33±20.81	45.81±21.04	0.721
Creatinine	84.56±15.99	83.61±17.88	84.09±27.89	80.97±21.70	0.543
Total Cholesterol	4.36±1.41	4.47±1.23	4.47±1.22	4.41±1.33	0.890
HDL-C	1.0±0.31	1.01±0.23	1.05±0.24	1.08±0.25	0.200
LDL-C	3.27±1.41	3.39±1.28	3.35±1.22	3.25±1.33	0.819
Triglycerides	1.70±0.91	1.83±1.07	1.73±1.05	1.70±0.97	0.748

AT, Atorvastatin and Ticagrelor (group AT) n=112; AC, Atorvastatin plus Clopidogrel n=108; RT, Rosuvastatin plus Ticagrelor n=133; RC Rosuvastatin plus Clopidogrel n=137; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCr, serum creatinine; ACEI, angiotensin‐converting enzyme inhibitors; ARB, angiotensin receptor blockers; PPI, protein pump inhibitors; HbA1c: Hemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol.

Table 2: Procedural characteristics.

Variables	AT	AC	RT	RC	P. Value
IRA, n (%)					
LM	4(3.5)	2(1.9)	1(0.8)	0(0)	0.102
LAD	43(38.4)	33(30.5)	56(42.1)	52(37.9)	0.024
LCX	25(22.3)	39(36.1)	40(30.1)	36(26.3)	0.130
RCA	40(35.7)	34(31.5)	38(28.6)	49(35.8)	0.544
Stents/patient	1.83±0.94	1.72±0.91	1.81±0.85	1.84±1.00	0.768
Total stent length (mm)	28.8±13.6	29.8±13.9	28.5±13.7	28.6±13.2	0.188
Stent diameter(mm)	3.11±0.42	3.13±0.41	3.17±0.45	3.16±0.38	0.514

AT, Atorvastatin and Ticagrelor (group AT) n=112; AC, Atorvastatin plus Clopidogrel n=108; RT, Rosuvastatin plus Ticagrelor n=133; RC Rosuvastatin plus Clopidogrel n=137; IRA, infarct-related artery; LMCA, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

Atorvastatin co-administration with ticagrelor was associated with a significant decrease of HCY levels after one year AT (20.45±9.26 vs.18.35±8.25), AC (20.59±8.36 vs.19.47±8.2), RT(17.47±6.74 vs.19.17±8.74), RC(18.25±7.39 vs.18.16±7.39), all P<0.05, respectively). MHR AT(0.69±0.32 vs. 0.25±0.09), AC (0.69±0.33 vs. 0.32±0.13), RT(0.65±0.31 vs. 0.35±0.31), RC(0.62±0.33 vs.0.52±0.33), NLR (2.79±1.44 vs. 1.72±1.40, 3.35±1.90 vs.2.15±1.12, 3.30±2.34 vs.2.31±1.34, 2.93±1.51 vs.1.13±0.91) at group AT, AC, RT, RC. all P<0.05, respectively. LVEF was more reduced in atorvastatin combined with ticagrelor group than other groups, P<0.05. For more details see Table 3.

Table 3: The effect of atorvastatin and rosuvastatin on laboratory parameters after 1-year treatment.

Variables	**AT n=112**	**AC n=108**	**RT n=133**	**RC n=137**	**P. Value**
Base-time					
Homocysteine	20.45±9.26	20.59±8.36	19.47±8.74	18.25±7.39	0.105
MHR	0.69±0.32	0.69±0.33	0.65±0.31	0.62±0.33	0.213
NLR	2.79±1.44	3.35±1.90	3.30±2.34	2.93±1.51	0.053
NT-proBNP	2386.5	2245.5	2459.0	3337.0	0.062
LAD	3.50	3.50	3.50	3.70	0.072
LVD	5.40	5.00	5.0	5.0	0.233
LVEF	52	51.50	53.0	53.00	0.352
After 1-year					
Homocysteine	18.35±8.25	19.47±8.2	17.17±6.74	18.16±7.39	0.015
MHR	0.25±0.09	0.32±0.13	0.35±0.31	0.52±0.33	0.013
NLR	1.72±1.40	2.15±1.12	2.31±1.34	1.13±0.91	0.043
NT-proBNP	500.0	900.0	612.0	915.0	0.032
LAD	3.65	3.53	3.6	3.6	0.112
LVD	5.0	4.70	4.85	4.8	0.215
LVEF	54.0	55.0	55.0	56.0	0.025

Data expressed as means ± S.D, or Median. MHR, Monocyte/HDL Cholesterol Ratio; NLR, Neutrophil/Lymphocyte Ratio; NT-proBNP, N-terminal pro b-type natriuretic peptide; LAD, left Atrium Diameter; LVD, Left Ventricular Diameter; LVEF, Left Ventricular Ejection Fraction.

Comparison of major efficacy endpoint events between the groups

The incidence rates of ischemic endpoint events (such as non-fatal myocardial infarction, cardiac death, symptoms with an urgent need for coronary revascularization, and cerebral stroke) within 12months were lower in the Atorvastatin plus clopidogrel combination group than in the other groups (3 (2.7%), 2(1.8%), 4(3.0%), and 3(2.2%) at groups AT, AC, RT, and RC) P<0.023. The occurrence rate of the major bleeding was similar in the groups AT, and RT (3 (2.6%), 2 (1.8%), 3 (2.2%), and 1 (0.7%) at AT, AC, RT, and RC groups, P<0.05, respectively. However, the differences noticed in the cardiac death, re-attack of myocardial infarction, urgent coronary revascularization, cerebral stroke, safety endpoint events, secondary bleeding events slight bleeding events were not statistically significant (P>0.05). See Table 4.

Table 4: Comparison of efficacy endpoint events between the two groups at 12months.

Variables	AT n=112	AC n=108	RT n=133	RC n=137	P. Value
Ischemic endpoint events, n (%)	3 (2.7)	2(1.8)	4(3.0)	3(2.2)	0.023
Cardiac death	1 (0.9)	2(1.8)	3(2.2)	5(3.6)	0.112
Re-Attack myocardial infarction	0(0.0)	1(0.9)	1(0.7)	3(2.2)	0.312
Urgent coronary revascularization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Cerebral stroke	1 (0.8)	1 (0.9)	2 (1.5)	1 (0.7)	0.546
Safety endpoint events, n (%)	8 (7.1)	6 (5.5)	7 (5.2)	7 (5.1)	0.612
Major bleeding events	3 (2.6)	2 (1.8)	3 (2.2)	1 (0.7)	0.034
Secondary bleeding events	8 (7.1)	5 (4.6)	7 (5.2)	3 (2.2)	0.115
Slight bleeding events	9 (8.0)	6 (5.5)	8 (6.0)	8 (5.8)	0.518

DISCUSSION

The present study represents one of several studies addressing the role of statin type on the platelet reactivity and the response to DAPT with ASA, clopidogrel and ticagrelor among patients with CAD. Our main finding is that among patients receiving dual antiplatelet therapy for CAD, the concomitant treatment with Atorvastatin or Rosuvastatin plus ticagrelor is associated with a decrease levels of homocysteine and NT-proBNP levels than with clopidogrel.

Applicable developments have been attained in the field of CAD, where developments in mechanical reperfusion strategies and innovations in pharmacological treatments have allowed to reduce mortality and the risk of recurrent cardiovascular events, especially in the settings of STEMI.[23,24] A potent platelet inhibition represents the pillar of anti-ischemic treatment, with a DAPT being recommended as soon as possible after an acute cardiovascular event or coronary stent implantation and indicated for at least 12 months in the majority of patients.

Atherosclerotic plaque rupture may induce an acute thrombosis inside the coronary arteries, this is the major reason of acute STEMI incidence, the pathophysiological differences including the platelet inflammatory factors and the vascular endothelium. The inflammatory factors, such as HCY, TNF-α, hs-CRP, 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 inflammatory process of the vasculature and the pathogenesis development of coronary atherosclerosis.[25] The occurrence of responsive inflammation consequence at the endothelial function vascular disorder, thinning and rupture of the atheromatous plaque fibrous cap but also triggering extrinsic coagulation paths, finally resulting in platelet aggregation and formation of thrombi.[26] An important role in both physiological and pathological processes shown by vascular endothelium, a monolayer of cells which covering the intima of the vessel. Physiologically, vascular endothelium plays a variety of important roles, including regulating blood flow, maintaining blood fibrinolysis and coagulation system balance, inhibiting vascular endothelial proliferation, chemotactic adhesion of inflammatory cells and platelet aggregation.[27] Under pathological conditions such as vascular endothelial dysfunction caused by endothelial damage, the above physiological balance is disrupted, resulting in chemotaxis of inflammatory cells, increased activity of inflammatory factors, white platelet aggregation and eventual thrombosis.[28] Vascular endothelial dysfunction has been proven to be one of the early factors affecting atherosclerosis, so early identification helps to assess and predict cardiovascular events, especially acute myocardial infarction.[29] Clopidogrel and ticagrelor are P2Y12 receptor antagonists, ticagrelor was launched late in the China market. Compared to clopidogrel, ticagrelor might, without metabolic stimulation, take effect directly after oral administration with a median of about 1.5 h, required to bind with the P2Y12 receptor reversibly and resulting in a fast recovery of platelets after drug withdrawal.[30] In addition to platelet membranes, P2Y12 receptors are also expressed on the surface of inflammatory cells. According to reports, in mice with P2Y12 receptor deficiency, the chemotaxis of inflammatory cells, including macrophages, is impaired.[31] In addition, many studies have shown that P2Y12 receptor antagonists can affect inflammatory cells by inhibiting P2Y12 receptors on the surface of inflammatory cells (such as microglia, neutrophils, dendritic cells, and monocytes). Migration[32,33], suggesting that ticagrelor may have other pharmacological effects in a similar manner.

In this study, we found that serum levels of HCY and MHR and NLR in the combination of Atorvastatin with ticagrelor group were lower than those in the other combinations' ether atorvastatin with clopidogrel or rosuvastatin with both ticagrelor or clopidogrel at 12 months after emergency PCI, ($P<0.05$). This indicates the superiority of ticagrelor to clopidogrel when combined with atorvastatin in the 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 can exert anti-inflammatory, anti-arteriosclerosis, anti-fibrosis and heart protection effects by increasing the concentration of ADP in the blood, which is consistent with the study of Jacobson et al.[34] Therefore, further

clinical research and experiments are needed to prove whether compared with clopidogrel, the P2Y12 receptor inhibitor ticagrelor or clopidogrel can further reduce serum inflammatory markers (such as HCY, hs-CRP or IL- 6) Level. The anti-inflammatory effect will provide clinical benefit to these patients.

The PLATO trial is a landmark study that conducted 18 624 patients from 43 countries and 862 centers for a two-year study. In our country, 416 patients participated in this study. The results (including the results of the invasive treatment subgroup) show that ticagrelor has a stronger platelet inhibitory effect on ACS patients than clopidogrel. The patient does not increase overall severe bleeding. However, the incidence of non-operative bleeding has increased.[35] In this study, the trend of efficacy endpoint events (ischemic endpoint events, safety endpoint events, and overall adverse events) in the four groups was similar to the PLATO trial. However, statistically significant difference was found in ischemic endpoint events when a combined therapy of the rosuvastatin and ticagrelor, major bleeding events was noticed more at atorvastatin plus ticagrelor treatment. More factors may be involved in the incidence of efficacy endpoint events, especially ischemic endpoint events, which will be further investigated and explored in the future.

Study Limitations

Our study has the following limitations: 1) The samples collected were only represent inpatients at that our center. 2) Due to the limited period of the study, the sample size collected is comparatively small, producing a certain deviation in the statistical results, particularly the results of effectiveness endpoint events where only ascending or descending tendency remnants, without a statistically significant alteration. 3) The duration of follow-up is short. Only a 12 months short-term follow-up was performed without a long-term follow-up on prediction. 5) A comparative study on the active changes of applicable parameters was performed in the 4 groups. Although a great significance at several time points on the basis of previous studies was observed, the active changes at multiple period 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 emergency PCI, 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, as compared with clopidogrel. Therefore, recommendation of ticagrelor should be used in the clinical practice.

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