

ARTICLE

The efficacy and safety of the short-term combination therapy with ticagrelor and PPIs or H2RA in patients with acute STEMI who underwent emergency PCI

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Abstract

Combination therapy with platelet inhibitors and acid-suppressive agents is recommended for patients with acute ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI), but there remains a paucity of data to evaluate both the efficacy and safety of these combinations. In this prospective study, a total of 170 patients with acute STEMI who underwent PCI were divided into four groups: pantoprazole + ticagrelor, omeprazole + ticagrelor, ranitidine + ticagrelor, and ticagrelor only. The risk of PCI, antithrombotic efficacy, cardiac function, and main end points were evaluated and compared. No significant differences were found in infarction-related artery perfusion indexes (thrombolysis in myocardial infarction [TIMI], corrected TIMI frame count), the incidence of stent thrombosis after PCI, platelet indicators (platelet count, mean platelet volume, and platelet distribution width), platelet activation (P-selectin and glycoprotein IIb/IIIa levels), platelet aggregation (thrombelastography indicators, such as ADP% and MA_{ADP}), myocardial necrosis biomarker (creatinine kinase isoenzyme-MB and cardiac troponin I) levels, brain natriuretic peptide levels, the incidence of ischemic end point events, and the incidence of other tissue and organ bleeding events among the four groups. The incidence of gastrointestinal (GI) bleeding events in the proton pump-inhibitor (PPI) group was significantly lower than that in the control group, whereas in the H2 receptor antagonist (H2RA) group it was not significantly different from the control group. The short-term combination therapy with ticagrelor and PPIs or H2RA is safe and effective in patients with acute STEMI after PCI. In addition, the PPIs combined with ticagrelor could reduce the incidence of GI bleeding events without increasing the incidence of ischemic events.

Peng Wei and Shujiang Zhuo contributed equally to this work as co-first authors.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The combined antiplatelet therapy for patients with acute ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI) increases the incidence of gastrointestinal (GI) complications, such as ulcers and GI bleeding. It is recommended that these patients are taking proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs) at the same time as antithrombotic therapy. However, there remains a paucity of data to evaluate both the efficacy and safety of these combinations.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to explore whether there are increased risks of stent thrombosis, other ischemic events, or a decreased antiplatelet effect when ticagrelor is combined with PPIs or H2RAs to prevent GI bleeding to find new economic, effective, and safe treatment.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study indicates that the application of PPIs or H2RAs in combination with ticagrelor is safe and effective in the treatment of patients with acute STEMI who underwent emergency PCI. The PPIs combined with ticagrelor could reduce the incidence of GI bleeding events without increasing the incidence of ischemic events.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides a clinical trial basis for rational drug use and laying the foundation for finding economical, effective, and safe new treatment of patients with acute STEMI who underwent emergency PCI.

INTRODUCTION

Acute coronary syndrome (ACS) is a clinical syndrome caused by acute myocardial ischemia (MI), including acute ST-segment elevation myocardial infarction (STEMI), acute non-ST-segment elevation myocardial infarction (non-STEMI), and unstable angina. Acute STEMI is the most critical type of ACS due to its rapid onset, dangerous progression, poor prognosis, and high fatality rate.¹ The rupture of the unstable coronary atherosclerotic plaque leading to thrombosis, severe MI, and even necrosis results in the onset of acute STEMI. The key to the successful therapy of acute STEMI is to open the infarction-related artery (IRA) as soon as possible to restore ischemic myocardium and reperfusion. With the development of drug-eluting stents, percutaneous coronary intervention (PCI) has become the first priority for the treatment of acute STEMI.^{2,3}

Platelet activation plays a key role in atherosclerotic plaque formation and thrombosis during acute STEMI. To reduce the risk of stent thrombosis and recurrent cardiovascular events after PCI, it is a consensus to use dual antiplatelet therapy (aspirin + ticagrelor or clopidogrel) before and after surgery.⁴ But the application of combined antiplatelet therapy also has its disadvantages, which is

to increase the incidence of gastrointestinal (GI) complications, such as ulcers and GI bleeding.^{5,6} However, abundant evidence showed that the high incidence of bleeding is mainly concentrated within 1 week of the disease course.⁷ Hence, it is important to choose the appropriate medications to prevent GI bleeding. It is recommended that patients with myocardial infarction take proton pump-inhibitors (PPIs) or H2 receptor antagonists (H2RAs) at the same time as antithrombotic therapy.⁸ However, the drug-drug interactions between PPIs and antiplatelet medications (such as omeprazole and clopidogrel) are controversial^{9,10} and remain a problem.¹¹⁻¹³ The combination therapy may result in increased inhibition of cytochrome P450 (CYP) enzymes and decreased clopidogrel antiplatelet effect.

Ticagrelor is a P2Y₁₂ reversible inhibitor. It does not require activation and is administered in its active form. Additionally, it does not undergo CYP2C19 metabolism, which is important for PPI co-administration.¹⁴ Ticagrelor exhibits better efficacy than clopidogrel.¹⁵⁻¹⁷ Previously, it has been demonstrated that in clopidogrel nonresponders switching to ticagrelor decreased platelet aggregation and improved the platelet resistance.¹⁶ In the PLATO clinical trial, the combinational use of ticagrelor and aspirin showed significantly fewer major end point events

(including cardiovascular death, myocardial infarction, or stroke) compared to the clopidogrel and aspirin combination (9.8% vs. 11.7%, $p = 0.0001$).¹⁷ Therefore, using ticagrelor could be a new option for antiplatelet therapy in acute STEMI situations. To prevent the bleeding risk of ticagrelor in antithrombotic applications, especially the risk of GI bleeding, PPIs or H2RAs are often used clinically for preventive intervention. However, reports on the comparative study of the interaction of ticagrelor with different PPIs or H2RAs in the treatment of acute STEMI are scarce.

This study aimed to investigate whether there are increased risks of stent thrombosis, other ischemic events, or a decreased antiplatelet effect when ticagrelor is combined with PPIs or H2RAs to prevent GI bleeding.

METHODS

Patients

This prospective study was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University, China. A total of 170 patients were hospitalized in our hospital due to acute ST-segment elevation myocardial infarction in September 2016 and received emergency coronary angiography (CAG) and PCI. There were 90 men and 80 women, aged 30–75 years old (mean: 60.51 ± 12.09). Based on the ticagrelor combination with PPIs or H2RAs at the time of treatment, the patients were divided into four groups: group A (PPI group), who received pantoprazole (group A1, 39 cases) or omeprazole (group A2, 43 cases); group B (H2RA group), who received ranitidine (43 cases); and group C, the control group (45 cases used ticagrelor only). All patients signed the informed consent form, and all selected patients were followed up by telephone during hospitalization and within 30 days after discharge.

Inclusion criteria

The inclusion criteria were: (1) aged 30–75 years old and indicated for emergency PCI surgery; (2) the STEMI diagnostic criteria comply with the 2010 Acute Myocardial Infarction Diagnostic Criteria of the Chinese Medical Association ([i] chest pain ≥ 30 minutes, symptoms cannot be significantly relieved after taking nitroglycerin; [ii] electrocardiogram in at least two limbs leads ST elevation ≥ 0.1 mV or adjacent pectoral leads ST elevation ≥ 0.2 mV; [iii] cardiac biomarkers [troponin I] increased, and at least one frequency value exceeded the 99th percentile of the upper limit of the reference value; i.e., the upper limit of normal); (3) the onset time does not exceed 12 h or the onset of more than 12 h still has chest tightness and pain

and continuous ST-segment elevation; (4) patients with acute myocardial infarction will not be given revascularization for non-criminal vascular disease (including other parts of the culprit's blood vessel of myocardial infarction and disease of the non-criminal blood vessel) within 30 days; and (5) the patient and family members agreed to participate in this clinical trial upon admission and signed a written informed consent form before the operation.

Exclusion criteria

The exclusion criteria were: (1) patients who have severe adverse reactions to ticagrelor and clopidogrel resistance, are allergic to aspirin, contrast agents, and use glycoprotein (GP) IIb/IIIa receptor antagonists; (2) patients who are not suitable for PCI based on clinical experience or previous examination judgment and CAG diagnosis; (3) patients with acute ST-segment elevation myocardial infarction within 24 h of left main disease, cardiogenic shock, and thrombolysis; (4) patients who have a history of PCI or coronary artery bypass graft surgery; (5) patients with high-risk bleeding or those with active bleeding and surgery or trauma within 3 months before enrollment; (6) patients who have taken PPIs or H2RAs within 1 week; (7) patients with abnormal blood routine (hemoglobin < 100 g/L, platelet count $< 100 \times 10^9$ /L); (8) patients with previous myocardial infarction or other heart diseases, and those with severe heart failure (New York Heart Association [NYHA] class III–IV); (9) patients with immune system diseases, such as diabetes and other endocrine diseases, digestive ulcers, acute and chronic infections, malignant tumors, hematological diseases, rheumatic connective tissue, etc.; (10) patients with cerebrovascular disease and peripheral vascular disease, etc.; (11) patients with obvious abnormal liver and kidney function (alanine aminotransferase and aspartate aminotransferase caused by non-myocardial infarction increased more than 3 times; blood creatinine level > 180 $\mu\text{mol/L}$); (12) patients who have a history of heparin-induced thrombocytopenia; (13) patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg); and (14) any other situation that the researcher speculated was not suitable for inclusion in the research.

Drug administration methods

Antiplatelet drug treatment

Aspirin (Bayaspirin, AG, Germany): a single dose of 300 mg followed by 100 mg once a day. Aspirin is to be taken for life if there is no contraindication.

Ticagrelor (Brilinta; AstraZeneca): a single dose of 180 mg followed by 90 mg twice a day until 12 months after surgery.

Medication in the study group and control group

Study group Patients were immediately given the corresponding PPIs or H2RAs orally on admission followed by routine dosing until discontinuation on day 7.

Group A1 Pantoprazole enteric-coated capsules (Huadong Medicine Co. Ltd.), a single dose of 40 mg followed by 40 mg once a day.

Group A2 Omeprazole enteric-coated capsules (Changzhou Siyao Pharmaceuticals Co. Ltd.), a single dose of 40 mg followed by 20 mg twice a day.

Group B Ranitidine hydrochloride capsules (Hengshan Pharmaceutical Co. Ltd.), a single dose of 300 mg followed by 150 mg twice a day.

Control group Patients were not given the corresponding PPIs or H2RAs.

Other drugs

Patients with indications were simultaneously given low molecular weight heparin, GPIIb/IIIa inhibitors, beta blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, calcium channel blockers, and nitrate esters for treatment.

Coronary intervention diagnosis and treatment (CAG + PCI)

After preprocedural preparations were made, CAG + PCI was carried out in a catheterization room equipped with a fully digital x-ray C-arm angiography machine (Koninklijke Philips N.V.). Transradial or transfemoral approaches were used, although the transradial approach was generally used. Routine disinfection, draping, and local anesthesia with lidocaine were carried out. After the radial artery was palpated and located, a needle was inserted at the site with the most visible pulsation using the Seldinger technique.

After fresh arterial blood was seen, the guidewire was inserted along the needle. The needle was then withdrawn when there was no resistance, and the guidewire

was retained. A 6F arterial sheath was inserted along the guidewire. The inner core and steel wire were removed, and 3000 U of heparin sodium was injected into the catheter. For CAG, 6FJL and 6FJR catheters were inserted into the openings of the left and right coronary arteries under the guidance of a J-shaped guidewire.

For imaging, 350 mg/ml of iohexol was used as the contrast agent. At least five projections (left anterior oblique caudal [“spider”], caudal, right anterior oblique caudal, anteroposterior cranial, and right anterior oblique cranial) were performed for the left coronary artery, and at least the left anterior oblique and cranial views were projected for the right coronary artery. Other projections were made when necessary to image the various coronary artery segments fully.

The above procedure was performed by an experienced clinical interventional cardiologist and assessed by two experienced interventional cardiologists. A visual inspection method that is used internationally was used to determine the degree of coronary artery stenosis (i.e., based on the percentage decrease in the diameter of the stenotic site compared with the internal diameter of normal coronary arteries at the distal and proximal ends of the stenotic segment). After a unanimous opinion was achieved and the result was determined, PCI was directly performed on the culprit vessel.

Observation markers

1. Infarction site (anterior wall myocardial infarction and non-anterior wall myocardial infarction).
2. Site of the infarction-related blood vessel (anterior descending branch, circumflex branch, or right coronary artery).
3. Duration from disease onset to balloon angioplasty or stent implantation (i.e., time to achieve coronary artery patency).
4. Pressure at maximum balloon dilatation.
5. Length and diameter of the implanted stent.
6. Thrombolysis in myocardial infarction (TIMI) risk score.
7. Transfemoral or transradial route.
8. Myocardial microcirculatory perfusion markers (TIMI blood flow grade and corrected TIMI frame count [CTFC]).
9. Stent thrombosis.

Collection of blood samples

Five ml of venous blood was immediately collected on admission (before dosing) and 24 h after taking the study

agents, and 5 ml of venous blood was collected on an empty stomach on the morning of day 7 after taking the study agents through the antecubital vein in all patients. During blood sampling, a tourniquet was not tied, and the blood vessel at the puncture site was not slapped. An effort was made to carry out blood sampling in one attempt. After the samples were collected, they were not shaken vigorously to prevent damaging platelets and hemolysis. The samples were processed according to experimental requirements, and relevant test markers were measured.

Measurement of relevant test markers

Three-item platelet test

The XE-2100D Hematology Analyzer (Sysmex Corp.) was used to measure the platelet count, mean platelet volume, and platelet distribution width immediately on admission, 24 h after taking the study agents, and on day 7 after taking the study agents through hydrodynamic focusing.

P-selectin (CD62P)

A human P-selectin enzyme-linked immunosorbent assay (ELISA) kit (CD62P, Shanghai Enzymelink Biotechnology Co., Ltd.) was used to measure CD62P levels according to the manufacturer's instructions.

Platelet membrane GPIIb/IIIa

Double-antibody sandwich ELISA was used to measure GP IIb/IIIa levels in the blood samples according to the manufacturer's instructions of the human platelet membrane glycoprotein ELISA kit (GP IIb/IIIa, Shanghai Lianshuo Biotechnology Co., Ltd.).

Thrombelastography

The TEG 5000 Thrombelastograph Analyzer (Haemoscope Inc.) and a platelet aggregation assay kit (coagulation method) were used according to the manufacturer's instructions. Five ml of blood was collected from each patient in a citrate tube immediately on admission and 2 h, and then on day 7 after taking the study agents. One ml of blood was added to tubes containing kaolin and was gently mixed (gentle inversion 5 times without vigorous shaking).

Following that, 360 μ l of the kaolin-processed blood samples were added to preheated sample cups (20 μ l of 0.2 M CaCl_2 was added for the citrate-treated blood samples to restore calcium) before the TEG 5000 Thrombelastograph Analyzer was used to measure the maximum amplitude generated by thrombin (MATHrombin). Ten ml of prepared activator F was added to two cups, and 10 μ l of arachidonic acid (AA) and adenosine diphosphate (ADP) were added. To the cups, 360 μ l of heparinized whole blood was added.

Then, the blood samples in the two cups were pipetted up and down thrice for mixing and the formation of platelet activator-activated whole blood cross-linked clots. The TEG 5000 Thrombelastograph Analyzer and its software were used to obtain AA%, MA_{AA} , ADP%, and MA_{ADP} in order to assess the effects of PPIs or H2RAs on the efficacy of ticagrelor.

Classical myocardial necrosis markers

The 7600-020 fully automated biochemical analyzer (Hitachi Ltd.) and creatine kinase isoenzyme-MB (CK-MB) kit (Shanghai Fosun Long March Medical Science Co., Ltd.) were used to detect the level of CK-MB in the four groups of patients at admission, 24 h after taking the study agents, and day 7 after taking the study agents by the immunosuppressive method. The Centaur CP chemiluminescence analyzer (Siemens AG, Germany) and cardiac troponin I (cTnI) kit (SIEMENS) were used to detect the level of cTnI in the four groups of patients at admission, 24 h after taking the study agents, and day 7 after taking the study agents by the chemiluminescence method.

Brain natriuretic peptide

Fresh peripheral blood was collected in ethylenediaminetetraacetic acid anticoagulant tubes immediately on admission and 24 h, and then on day 7 after taking the study agents. The Triage fluorescence immunoanalyzer (Biosite Inc.) was used to measure brain natriuretic peptide (BNP) levels according to the instructions.

IRA perfusion index

Coronary TIMI blood flow refers to the blood flow of the relevant coronary vessels during heart muscle infarction, which can be divided into 0–III levels, a total of four levels, through coronary angiography based on the following criteria: TIMI level 0: no irrigation (no forward blood flow [contrast agent] filling of the lesions and distant blood vessels); TIMI level I: micro-irrigation (the contrast agent

can pass through the site of the lesions, but does not pass through the far-end blood vessels); TIMI level II: partial irrigation (the contrast agent can pass through the lesions section, and reach the far end of the lesions of blood vessels, but its filling speed in normal blood vessels is significantly slower); TIMI level III: complete irrigation (the contrast agent can completely and rapidly fill the lesions blood vessels). CTFC is also used as an indicator of the IRA perfusion index. CTFC is calculated as TIMI frame count (TFC) divided by 1.7. The TFC is obtained by counting the number of frames required for coronary arteries to begin to be tinted to a standardized distal marker development during CAG.

End points

Ischemic end point

The patients in the groups were followed up during hospitalization and within 30 days after discharge. Their primary ischemic end point events (cardiogenic death, non-fatal myocardial infarction or stroke, and requiring emergency coronary revascularization) and secondary ischemia end point events (the single component of primary ischemic end point events) were counted.

Safety end point (bleeding)

Regarding TIMI bleeding classification¹⁸ and PLATO test,¹⁹ safety end points include (1) GI bleeding events ([i] occult bleeding: the occult blood test is positive without obvious bleeding; [ii] heavy GI bleeding: obvious hematemesis, hematochezia, or significantly decreased hemoglobin [>5 g/dl], significantly decreased hematocrit [greater than 15%]; and [iii] minor bleeding: between hidden bleeding and GI bleeding); (2) bleeding events in other tissues and organs—except for GI bleeding—any bleeding in tissues and organs, including life-threatening and non-life-threatening bleeding.

Statistical analysis

SPSS version 22.0 was used for statistical analysis. Measurement data were presented as mean \pm SD. One-way analysis of variance test was used for comparison between groups, and SNK-q was used for pairwise comparison between multiple groups. Count data are presented as the number of cases/percent ($n/\%$), and the comparison of multisample rates was analyzed by χ^2 test or Fisher's exact probability method.

RESULTS

Comparison of baseline characteristics in each group

There were no significant differences in gender, age, body mass index, cardiovascular risk factors (smoking history, drinking history, history of hypertension, family history of coronary heart disease, total cholesterol, low-density lipoprotein cholesterol, and triglycerides), medication during the study (whether to use low molecular weight heparin, glycoprotein IIb/IIIa inhibitors, β -receptor blockers, angiotensin-converting enzyme inhibitors [ACEI]/ angiotensin receptor blockers [ARBs], statins, calcium channel blockers [CCBs], and nitrate medications), aspartate aminotransferase, alanine aminotransferase, creatinine, blood urea nitrogen, stress blood glucose, and cardiac ejection fraction value of patients in each group ($p > 0.05$; Table 1).

Comparison of myocardial infarction-related indicators in each group

No significant differences were found in the infarct location, infarct-related blood vessel location, coronary artery patency time, maximum balloon inflation pressure, the length and diameter of the implanted stent, and TIMI risk score among each group of patients ($p > 0.05$; Table 2).

Comparison of IRA perfusion indexes in each group

No significant differences were observed in the incidence of TIMI blood flow classification and CTFC among each group of patients ($p > 0.05$; Figure 1a,b).

Comparison of incidence of stent thrombosis after PCI in each group

No cases of confirmed or possible acute stent thrombosis were found. Two cases of confirmed or possible subacute stent thrombosis were found, including one case in group A (1 case in group A1 and 0 case in group A2) and one case in group C. No significant differences in the incidence of acute stent thrombosis or subacute stent thrombosis were found among each group ($p > 0.05$). There was also no statistically significant difference in the total incidence of stent thrombosis between groups ($p > 0.05$; Table 3).

TABLE 1 Baseline characteristics of the patients in the study

	Group A1 (N = 39)	Group A2 (N = 43)	Group B (N = 43)	Group C (N = 45)	p value
Gender (male/female)	21/18	22/21	23/20	24/21	0.995
Age (year)	61.74 ± 12.12	60.40 ± 12.47	60.72 ± 11.63	59.36 ± 12.44	0.844
BMI (kg/m ²)	25.90 ± 3.13	25.07 ± 2.47	25.95 ± 2.64	25.67 ± 2.52	0.405
Cardiovascular risk factors n (%)					
Smoking	19 (48.7)	22 (51.2)	20 (46.5)	24 (53.3)	0.928
Alcoholic	26 (66.7)	28 (65.1)	28 (65.1)	31 (68.9)	0.979
Hypertension	15 (38.5)	16 (37.2)	14 (32.6)	18 (40.0)	0.902
Family history of CHD	4 (10.3)	4 (9.3)	3 (7.0)	5 (11.1)	0.922
TC (mmol/L)	4.73 ± 1.04	4.76 ± 1.09	4.65 ± 1.05	4.63 ± 1.09	0.930
LDL-C (mmol/L)	3.18 ± 0.67	3.21 ± 0.61	3.15 ± 0.75	3.18 ± 0.78	0.978
TG (mmol/L)	1.34 ± 0.49	1.32 ± 0.48	1.37 ± 0.47	1.31 ± 0.46	0.939
Medication n (%)					
Low-molecular-weight heparin	39 (100.0%)	43 (100.0%)	43 (100.0%)	45 (100.0%)	—
Glycoprotein IIb/IIIa inhibitors	16 (41.0%)	16 (37.2%)	18 (41.9%)	20 (44.4%)	0.922
β-receptor blockers	20 (51.3%)	23 (53.5%)	20 (46.5%)	28 (62.2%)	0.513
ACEI	11 (28.2%)	13 (30.2%)	13 (30.2%)	16 (35.6%)	0.897
ARB	1 (2.6%)	1 (2.3%)	1 (2.3%)	2 (4.4%)	0.999
Statins	39 (100.0%)	43 (100.0%)	43 (100.0%)	45 (100.0%)	—
CCB	14 (35.9%)	15 (34.9%)	14 (32.6%)	12 (26.7%)	0.798
Nitrate medications	23 (59.0%)	26 (60.5%)	20 (46.5%)	27 (60.0%)	0.505
Blood test					
AST (u/L)	38.03 ± 6.26	39.81 ± 7.17	40.09 ± 5.89	39.58 ± 6.66	0.491
ALT (u/L)	35.44 ± 6.42	34.95 ± 5.50	34.05 ± 5.56	34.93 ± 6.07	0.751
Creatinine (umol/L)	87.09 ± 17.48	85.91 ± 13.87	88.14 ± 15.22	87.54 ± 16.94	0.929
BUN (mmol/L)	7.09 ± 2.30	7.20 ± 2.21	6.51 ± 2.65	7.02 ± 2.54	0.573
Stress blood glucose (mmol/L)	7.39 ± 2.97	7.50 ± 2.76	7.76 ± 2.61	7.50 ± 2.82	0.941
EF	0.53 ± 0.07	0.49 ± 0.08	0.50 ± 0.08	0.50 ± 0.07	0.264

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel antagonist; CHD, coronary heart disease; EF, ejection fraction; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Comparison of platelet indicators in each group

No significant differences were found in the platelet indicators (platelet count [PLT], mean platelet volume [MPV], platelet distribution width [PDW]) among the four groups of patients at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$; Table 4).

Comparison of P-selectin and GP IIb/IIIa levels in each group

The levels of P-selectin and GP IIb/IIIa of the patients in each group increased at 24 h after taking the study agents, and all

showed a downward trend on the seventh day after taking the study agents. No significant differences were found in the P-selectin and GP IIb/IIIa levels among the four groups of patients at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$; Figure 1c,d).

Comparison of TEG indicators in each group

No significant differences were found in the platelet inhibition rate (ADP%) and platelet aggregation rate (MA_{ADP}) of the ADP pathway among each group of patients at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$; Figure 1e,f).

TABLE 2 Myocardial infarction-related indicators in each group

	Group A1 (N = 39)	Group A2 (N = 43)	Group B (N = 43)	Group C (N = 45)	p value
Infarct location n (%)					
Anterior myocardial infarction	20 (51.3%)	22 (51.2%)	18 (41.9%)	25 (55.6%)	0.627
Non-anterior myocardial infarction	19 (48.7%)	21 (48.8%)	25 (58.1%)	20 (44.4%)	0.627
Infarct-related blood vessels n (%)					
Anterior descending branch	20 (51.3%)	22 (51.2%)	21 (48.8%)	23 (51.1%)	0.995
Circumflex	7 (17.9%)	8 (18.6%)	8 (18.6%)	7 (15.6%)	0.979
Right coronary artery	12 (30.8%)	13 (30.2%)	14 (32.6%)	15 (33.3%)	0.988
Coronary artery patency time (h)	4.41 ± 1.01	4.32 ± 1.05	4.20 ± 1.00	4.30 ± 1.09	0.838
Maximum balloon inflation pressure (atm)	10.21 ± 2.24	10.21 ± 2.02	10.28 ± 2.14	10.24 ± 2.20	0.998
Stent length (mm)	20.79 ± 5.38	20.88 ± 4.85	21.05 ± 4.58	21.00 ± 5.11	0.996
Stent diameter (mm)	2.96 ± 0.27	2.95 ± 0.35	2.94 ± 0.33	2.97 ± 0.32	0.960
TIMI risk score-- high-risk n (%)	16 (41.0%)	19 (44.2%)	17 (39.5%)	22 (48.9%)	0.823
Femoral artery path n (%)	7 (17.9%)	8 (18.6%)	6 (14.0%)	9 (20.0%)	0.895

Abbreviation: TIMI, thrombolysis in myocardial infarction.

Comparison of myocardial necrosis biomarker (CK-MB and cTnI) and BNP levels in each group

The levels of typical myocardial necrosis markers (CK-MB and cTnI) and BNP levels of patients in each group increased at 24 h after taking the study agents, and all the levels showed a downward trend on the seventh day after taking the study agents. No significant differences were found in CK-MB, cTnI, and BNP levels among groups at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$; Figure 1g–i).

Comparison of main end points in each group

No significant differences were found in the incidence of ischemic end point events (including cardiac death, non-fatal myocardial infarction, emergency coronary revascularization, and stroke) among each group of patients (including subgroup A) within 30 days ($p > 0.05$; Tables 5 and 6). About the safety end point events, the incidence of GI bleeding events in each group of patients was not exactly the same ($p < 0.05$). The incidence of GI bleeding events in the combination treatment groups (group A and group B) were lower than that in the control group (group C). After pairwise comparison, this incidence of patients in group A was significantly lower than that in group C ($p < 0.05$; Table 5). There was no significant difference in this incidence of the patients between group A and group

B and between group B and group C ($p > 0.05$), and there was also no significant difference in this incidence of the patients among the subgroups of group A (group A1 and group A2), group B, and group C ($p > 0.05$; Tables 5 and 6). There was also no significant difference in the incidence of other tissue and organ bleeding events of patients in each group (including subgroup A, $p > 0.05$; Tables 5 and 6).

DISCUSSION

We indicated that the short-term combination use of ticagrelor and PPIs or H2RAs neither reduced the antiplatelet effect nor increased the occurrence of slow or no-reflow events. Such combination therapy would not generate new damage to cardiac function and affect cardiac function in our observation. Moreover, the combination therapy with ticagrelor and PPIs could reduce the incidence of GI bleeding events without increasing the incidence of ischemic events.

PPIs are benzimidazole derivatives, mainly including omeprazole, lansoprazole, pantoprazole, rabeprazole, etc. It is currently believed that PPIs, in addition to suppressing gastric acid secretion, may also have anti-inflammatory and antioxidant effects in the treatment of acid-related diseases.^{20,21} H2RAs can inhibit the secretion of gastric acid and pepsin by blocking the binding of H₂ receptors in gastric mucosal cells that secrete gastric acid to histamine and other substances, thereby reducing the gastric juice volume and hydrogen

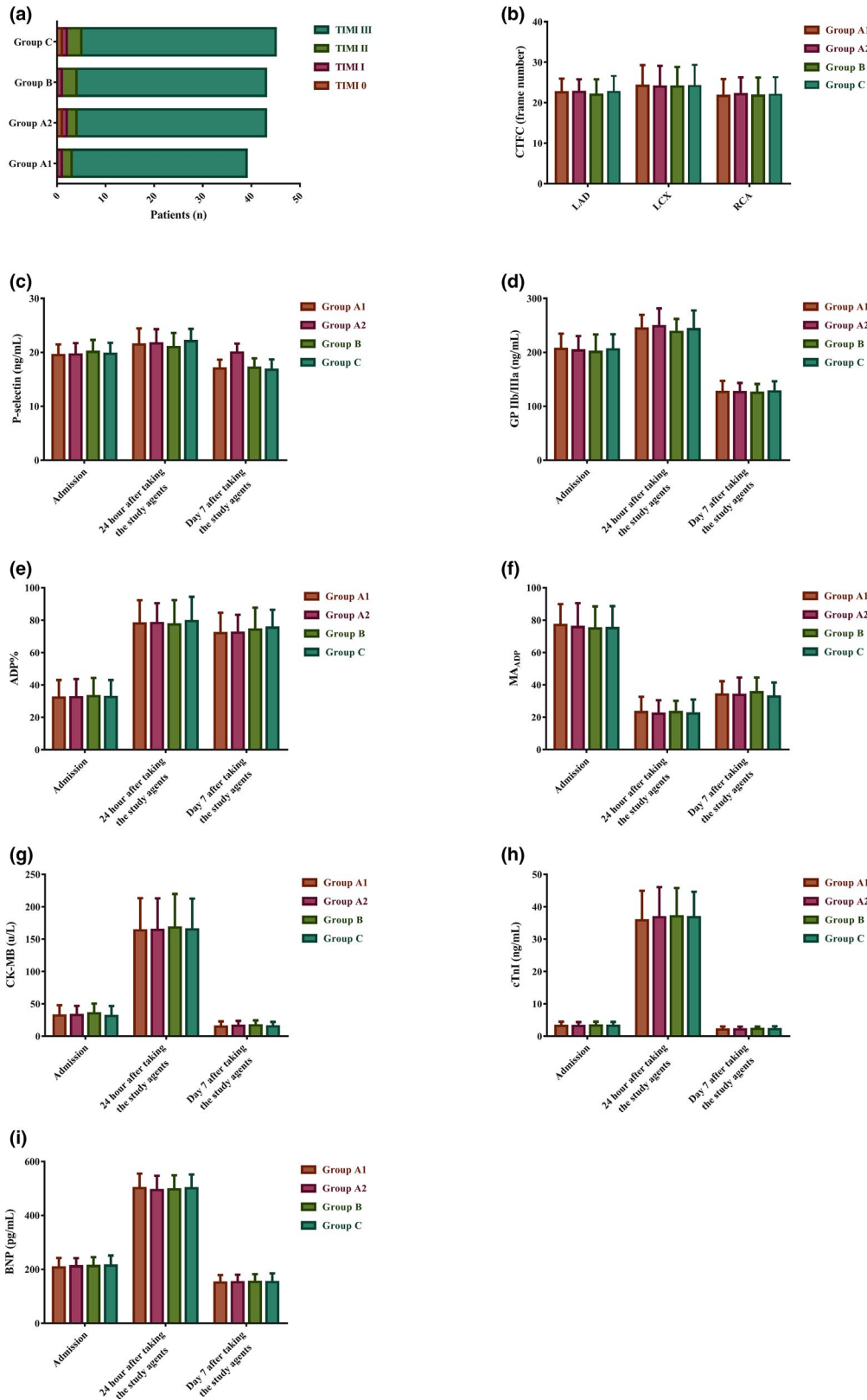


FIGURE 1 Comparison of thrombolysis in myocardial infarction (TIMI) blood flow classification (a), corrected TIMI frame count (CTFC) (b), P-selectin level (c), glycoprotein (GP) IIb/IIIa level (d), platelet inhibition rate (ADP%) (e), platelet aggregation rate (MA_{ADP}) (f), creatine kinase isoenzyme-MB (CK-MB) level (g), cardiac troponin I (cTnI) level (h), and brain natriuretic peptide (BNP) level (i) in each group

TABLE 3 Incidence of stent thrombosis after PCI in each group

	Group A1 (N = 39)	Group A2 (N = 43)	Group B (N = 43)	Group C (N = 45)	p value
Acute stent thrombosis n (%)					
Confirmed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Confirmed or possible	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Subacute stent thrombosis n (%)					
Confirmed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Confirmed or possible	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.602
Total stent thrombus n (%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.602

Abbreviation: PCI, percutaneous coronary intervention.

TABLE 4 Platelets indicators in each group

	Group A1 (N = 39)	Group A2 (N = 43)	Group B (N = 43)	Group C (N = 45)	p value
PLT (*10 ⁹ /L)					
At admission	167.90 ± 35.04	166.44 ± 43.18	164.42 ± 36.32	163.98 ± 38.01	0.963
24 h after taking the study agents	159.72 ± 39.10	157.14 ± 33.44	156.93 ± 36.96	159.02 ± 38.25	0.982
Day 7 after taking the study agents	204.46 ± 56.04	209.60 ± 43.34	208.91 ± 52.14	212.00 ± 45.25	0.918
MPV (fL)					
Hospitalized	11.64 ± 1.29	11.43 ± 1.15	11.72 ± 1.32	11.65 ± 1.32	0.743
24 h after taking the study agents	12.61 ± 1.29	12.41 ± 1.27	12.61 ± 1.63	12.59 ± 1.29	0.897
Day 7 after taking the study agents	10.56 ± 1.14	10.39 ± 1.03	10.53 ± 1.46	10.58 ± 1.19	0.884
PDW (fL)					
Hospitalized	15.84 ± 3.44	15.53 ± 2.22	15.87 ± 2.53	16.02 ± 3.08	0.879
24 h after taking the study agents	16.81 ± 3.83	16.26 ± 2.66	16.37 ± 2.81	16.29 ± 3.20	0.853
Day 7 after taking the study agents	13.72 ± 3.03	14.27 ± 2.97	13.65 ± 2.73	13.57 ± 2.73	0.662

Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width; PLT, platelet count.

ion concentration, and antagonizing the vasodilation effect of histamine, protecting the gastric mucosa.²² There are currently four generations of such drugs used in clinical practice. The PPIs selected in this study were omeprazole and pantoprazole. The main catalytic enzymes for their liver metabolism are CYP2C19 and/or CYP3A4. The pantoprazole can also be metabolized by the phase II metabolic bypass of sulfotransferase. Drug interactions are not prone to occur. The H2RA chosen in this study was ranitidine, which has small side effects; and only 30% of ranitidine taken is metabolized by the liver. The three drugs are economical, practical, and easy to accept by patients and their families. At the same time, they have their own different liver enzyme competitive inhibition characteristics for the metabolic mechanism of ticagrelor and have good representativeness. In 2019, the US Food and Drug Administration (FDA) recalled ranitidine medicines because some ranitidine medicines might contain low levels of the probable human carcinogen N-nitrosodimethylamine

(NDMA).²³ In April 2020, the FDA requested the complete withdrawal of ranitidine from the market on the grounds that when stored at high temperatures, NDMA levels may increase.²⁴ However, there is no long-term epidemiological studies on the risk of cancer caused by long-term exposure to NDMA from specific drugs. Some studies have shown that there was no increase in the risk of various cancers after taking ranitidine. In addition, a few studies that evaluated the cancer risk of ranitidine were flawed.²⁴ Therefore, more studies are needed on the safety of ranitidine. These circumstances were not known when we conducted the study in 2016, and the ranitidine was considered safe at that time. Compared with H2RAs, PPIs have high specificity, have a strong and long-lasting effect on inhibiting gastric acid, and can more effectively reduce the risk of GI bleeding caused by antiplatelet therapy.²⁵

TIMI blood flow classification and CTFC are currently commonly used effective methods to evaluate the vascular perfusion of criminal vessels in patients with myocardial

TABLE 5 Summary of main end points in groups A, B, and C

	Group A (N = 82)	Group B (N = 43)	Group C (N = 45)	p value
Ischemic end point events <i>n</i> (%)	2 (2.4%)	1 (2.3%)	1 (2.2%)	0.999
Cardiac death	1 (1.2%)	0 (0.0%)	0 (0.0%)	0.999
Non-fatal myocardial infarction	1 (1.2%)	0 (0.0%)	1 (2.2%)	0.999
Emergency coronary revascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Stroke	0 (0.0%)	1 (2.3%)	0 (0.0%)	0.253
Safety end point events <i>n</i> (%)	2 (2.4%)	2 (4.7%)	5 (11.1%)	0.115
Gastrointestinal bleeding events <i>n</i> (%)	0 (0.0%) ^a	1 (2.3%)	4 (8.9%)	0.013
Occult bleeding	0 (0.0%)	1 (2.3%)	2 (4.4%)	0.136
Minor bleeding	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.518
Heavy bleeding	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.518
Other tissue and organ bleeding events <i>n</i> (%)	2 (2.4%)	1 (2.3%)	1 (2.2%)	0.999
Total adverse events <i>n</i> (%)	4 (4.9%)	3 (7.0%)	6 (13.3%)	0.237

^a*p* < 0.05 compared with group C.**TABLE 6** Summary of main end points in groups A1, A2, B, and C

	Group A1 (N = 39)	Group A2 (N = 43)	Group B (N = 43)	Group C (N = 45)	p value
Ischemic end point events <i>n</i> (%)	1 (2.6%)	1 (2.3%)	1 (2.3%)	1 (2.2%)	0.999
Cardiac death	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0.735
Non-fatal myocardial infarction	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.602
Emergency coronary revascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Stroke	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0.735
Safety end point events <i>n</i> (%)	1 (2.6%)	1 (2.3%)	2 (4.7%)	5 (11.1%)	0.337
Gastrointestinal bleeding events	0 (0.0%)	0 (0.0%)	1 (2.3%)	4 (8.9%)	0.058
Occult bleeding	0 (0.0%)	0 (0.0%)	1 (2.3%)	2 (4.4%)	0.619
Minor bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.602
Heavy bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.602
Other tissue and organ bleeding events <i>n</i> (%)	1 (2.6%)	1 (2.3%)	1 (2.3%)	1 (2.2%)	0.999
Total adverse events <i>n</i> (%)	2 (5.1%)	2 (4.7%)	3 (7.0%)	6 (13.3%)	0.489

infarction. Compared with the TIMI blood flow classification, CTFC is less affected by the clinical experience of coronary interventional doctors and is more objective and accurate.²⁶ In this study, the results showed that no significant differences were found in the TIMI blood flow classification, CTFC, and the incidence of acute stent thrombosis or subacute stent thrombosis and the total incidence of

stent thrombosis in each group (*p* > 0.05), suggesting that the PPI or H2RA application was safe.

Platelet activation plays an extremely important role in the development of acute STEMI. The levels of P-selectin and GPIIb/IIIa are indicators of platelet activation and the degree of activation.²⁷ In this study, no significant differences were observed in the levels of P-selectin, and GP IIb/

IIIa among the groups at the three time points during the therapy ($p > 0.05$). Furthermore, the levels of three routine platelet items (PLT, MPV, and PDW) of patients in each group showed no significant difference at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$). Therefore, the effect of the combination therapy on the number and volume of platelets was eliminated, that is, the interference of platelet number and volume on platelet activation and aggregation was eliminated. These results suggest that the PPIs or H2RAs combined with ticagrelor did not negatively affect the antithrombotic efficacy of ticagrelor. The platelet aggregation can better reflect the clinical efficacy of antiplatelet drugs and the effects of other drugs on the effect of platelets. We have used the more commonly used TEG method for blood dynamic evaluation of platelet aggregation in the whole process. TEG indicators reflect the plasma coagulation dynamics (including the rate of fibrin formation, dissolution, firmness of coagulation, and elasticity).²⁸ The results in this study suggested there were no significant differences in ADP% and MA_{ADP} at admission, 24 h after taking the study agents, and day 7 after taking the study agents ($p > 0.05$). Our findings indicated that ticagrelor combined with different PPIs or H2RAs did not affect the platelet aggregation inhibition rate in patients with acute STEMI who underwent PCI, once again proving that the application of PPIs or H2RAs is safe for antithrombotic treatment of ticagrelor.

We also verified the impact of the combination therapy on the myocardial necrosis biomarker (CK-MB and cTnI) and cardiac function (BNP). No significant difference could be found in the levels of CK-MB, cTnI, and BNP among groups, suggesting that the combination therapy neither aggravated MI and hypoxia, nor increased ventricular load and wall tension in patients with acute myocardial infarction. It could be concluded that such combination therapy did not affect the cardiac function.

We analyzed the ischemic end point and safety end point of the combination therapy, referring to the PLATO trial.¹⁹ There was no significant difference in the incidence of ischemic end point events (including cardiac death, non-fatal myocardial infarction, emergency coronary revascularization, and stroke) within 30 days and the incidence of other tissue and organ bleeding events among groups ($p > 0.05$). There was no statistically significant difference in the incidence of GI bleeding events between the H2RA group and the control group. In addition the incidence of GI bleeding events in the PPI group was significantly lower than that in the control group ($p < 0.05$).

This study has some limitations. It was a single-center research and was limited by the small number of samples collected due to the limitation of the study time. This may lead to insignificant statistical results of ischemic end

point events. Further, the short-term 30 days of follow-up was not sufficient to assess the long-term prognosis. The few significant time points (at admission, 24 h after taking the study agents, and day 7 after taking the study agents) were selected due to funding limitations.

CONCLUSIONS

The study showed that the short-term application of different PPIs or H2RAs did not reduce the antiplatelet efficacy of ticagrelor and did not increase the occurrence of slow or no-reflow events. The PPIs or H2RAs combined with ticagrelor showed no new damage to the myocardium or cardiac function. The PPIs combined with ticagrelor could reduce the incidence of GI bleeding events without increasing the incidence of ischemic events. These findings indicate that the application of PPIs or H2RAs in combination with ticagrelor is safe and effective in the treatment of patients with acute STEMI who underwent emergency PCI, providing a clinical trial basis for rational drug use and laying the foundation for finding economical, effective, and safe new treatments.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.W. and S.J.Z. wrote the manuscript. L.S.W., B.M.C., and P.W. designed the research. P.W., Q.F., H.B.W., and B.Z., performed the research. S.J.Z. and B.M.C. analyzed the data. P.W. and L.S.W. contributed new reagents/analytical tools.

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