Clopidogrel Versus Ticagrelor in the Treatment of Patients Undergoing Percutaneous Coronary Intervention: Effects on Platelet Function Assessed by Platelet Function Tests and Mean Platelet Volume.

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Research

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Abstract

Background: Knowledge on the pharmacodynamic effects of antiplatelet drugs including clopidogrel and ticagrelor on Asian patients is scarce. We aim to evaluate the effects of the two drugs on platelet reactivity in the treatment of Chinese patients who underwent percutaneous coronary intervention (PCI), using two platelet function tests (PFT). Meanwhile, the relationship between mean platelet volume (MPV), a routinely index of platelet size, and high on-treatment platelet reactivity (HPR) is also investigated.

Methods: Patients receiving dual antiplatelet therapy (DAPT) treatment were scheduled for the assessment of platelet reactivity at 2-3 days after PCI. Two PFTs, light transmission aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) assay, were applied in the evaluation of platelet reactivity. MPV was measured simultaneously.

Results: The final study population included the traditional therapy group with aspirin and clopidogrel (n = 46) and the new therapy group with aspirin and ticagrelor (n = 66). In the new therapy group, the value of platelet aggregation assessed by LTA was obviously lower than that in the traditional therapy group (P < 0.001). The platelet reactivity index (PRI) level at VASP test was also markedly lower in the group given the new therapy (P < 0.001). It presented significant difference of HPR rates between the two groups. MPV showed a potent ability in predicting the presence of HPR at VASP assay (AUC = 0.788, 95% CI: 0.701-0.875, P < 0.001) in receiver-operating characteristic curve analysis.

Conclusions: Compared with clopidogrel, ticagrelor has dramatically greater antiplatelet effect, with a superiority of suppressing platelet function and a lower HPR rates. In addition, there existed a significantly independent association between MPV and high prevalence of HPR at VASP assay.

1. Introduction

It is known that dual antiplatelet therapy (DAPT) which is consisted of aspirin and one of P2Y12 receptor antagonists has been used for secondary prevention of thrombotic events, particularly in acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI) with stenting[1, 2]. Clopidogrel, the popular P2Y12 receptor inhibitor, is most widely used. However, the wide inter- and intra-individual variability in clopidogrel response represents a significant clinical limitation[3, 4], and high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) is now regarded as a well-established marker reflecting the thrombotic recurrence risk[5, 6]. In comparison with clopidogrel (a thienopyridine P2Y12R antagonist), which can bind irreversibly to the ADP receptor, ticagrelor, a novel non-thienopyridine ADP antagonist, reversibly inhibits the ADP P2Y12 receptor located on platelets, preventing platelet activation and aggregation[7]. To date, most clinical studies have demonstrated that ticagrelor can provide a more rapid effect of platelet inhibition and a more favorable pharmacodynamic profile when compared with clopidogrel[8, 9]. In addition, it has been recommended in the current guideline that new DAPT with aspirin and ticagrelor can be administered to patients with ACS after stenting (IIA)[10]. Unfortunately, few Asian patients were included in the studies that investigated the responses to clopidogrel and ticagrelor.

Therefore, exploring the effects of the two popular antiplatelet drugs on platelet function in Asian patients is increasingly urgent.

Platelet activation by ADP is central to the development of atherothrombosis. Platelet function tests (PFT) play an important role in evaluating individual antiplatelet drug responses and the therapeutic effects of different treatments. Therefore, PFT are recommended to guide the clinical treatment of patients with high risk factors for ischemia and those undergoing PCI or who have poor drug compliance[11]. In recent years, platelet reactivity has been measured by various systems for PFT[12]. Modern laboratory techniques including platelet function analyzer (PFA), the VerifyNow P2Y12 assay, light-transmission aggregometry (LTA), multiple electrode platelet aggregometry (MEA), thromboelastography (TEG) and vasodilator-stimulated phosphoprotein (VASP) assay, are all applied to measure different properties associated with platelet reactivity, with different detection principles. LTA, invented by Born[13], is the oldest available method in platelet activation assessment and was regarded as the “gold standard”[14]. The VASP assay was based on flow cytometric measurement of the VASP phosphorylation level[15]. Furthermore, mean platelet volume (MPV), which is a common index indicating platelet size, has been recommended as a marker of platelet activity[16]. However, the role of MPV in evaluating HPR rates in patients with stents is still debated, because contrasting results have been reported so far on the relationship between platelet size and aggregation[17–19].

Therefore, our present study aimed to evaluate the pharmacodynamic effects of clopidogrel and ticagrelor on Chinese patients undergoing PCI, with LTA and VASP assay assessing platelet function. We also investigated the relationship between MPV and HPR among patients receiving DAPT treatment.

2. Methods

2.1 Study design

For this study, we consecutively enrolled 112 patients presenting to Fuwai Hospital (Beijing, China) undergone PCI for the assessment of platelet function from March 2017 to June 2017. The procedure followed of this study was in accordance with standard ethical principles according to the Declaration of Helsinki. Consecutive participants were enrolled in line with the following inclusion criteria: age > 18 years; had undergone PCI with drug-eluting stenting. The exclusion criteria were as follows: a history of coronary artery transplantation or bypass graft; use of glycoprotein IIb/IIIa receptor inhibitors or other ADP receptor antagonists; infection; renal failure undergoing dialysis; history of drug allergy; bleeding; and genetic history. Diagnosis and performance of PCI were based on standard practices. The participants were divided into two groups: the traditional therapy group (aspirin + clopidogrel) (n = 46) and the new therapy group (aspirin + ticagrelor) (n = 66) according to different clinical therapy methods. The choose of DAPT depended on patients' clinical characteristics and evaluations of clinicians in accordance with 2017 ESC guideline[20]. Patients received aspirin (100 mg once daily) and clopidogrel (75 mg once daily) or ticagrelor (90 mg twice daily) on the day of PCI for at least 1 year. Additional file 1 (Fig. S1) has shown the flow chart of our study design.

2.2 Clinical data collection

Patients' basic information including age and sex were recorded on admission. The clinical characteristic information including body mass index (BMI), left ventricular ejection fraction (LVEF), history of diseases and medication were also recorded simultaneously. Patients were scheduled for biochemistry and platelet function testing at 2–3 days after PCI. The hemoglobin (Hb), platelet count (PLT) and MPV were measured using a Sysmex XN 2000 automated hematology analyzer (Sysmex, Kobe, Japan) and appropriate reagents; serum low-density lipoprotein-cholesterol (LDL-C), high-sensitivity C-reactive protein (hsCRP), alanine transaminase (ALT) and aspartate transaminase (AST) were assayed by an Olympus AU-5400 biochemistry autoanalyzer (Olympus Corporation, Mishama, Japan); the value of LVEF was determined via chest X-radiography and echocardiography.

2.3 Platelet function measurement

2.3.1 Light transmittance aggregometry

Blood samples were collected in 3.2% sodium citrate tubes (Becton-Dickinson, San Jose, CA, USA) within 2 h [21]. The blood was centrifuged 120 × *g* for 10 min to acquire the supernatant as platelet-rich plasma. Then, platelet-poor plasma was obtained after another centrifugation at 1500 × g for 15 min for the remaining blood. AggRam aggregometer (Techlink, Biomedical Technology Co., Ltd, Beijing, China) was applied to detect platelet aggregation at 37 °C. 5 μmol/L ADP was used to stimulate platelets. The maximum percentage change in light transmittance from baseline, based on the reference of platelet-poor plasma was regarded as the result of aggregation.

2.3.2 Vasodilator-stimulated phosphoprotein assay

The VASP assay was carried out by an experienced technician within 24 hours. Platelet VASP kits were used to determine VASP phosphorylation according to the manufacturer's instructions (Diagnostica Stago, Asnières, France). Briefly, blood samples were collected in 3.2% sodium citrate tubes. Fixation was performed after incubated with ADP and/or prostaglandin E_1 (PGE_1) *in vitro*. In the process of indirect immunolabeling, each sample was incubated with 16C2 monoclonal antibody and then stained with a goat anti-mouse fluorescein isothiocyanate polyclonal antibody. Flow cytometric measurement was performed via a cytometer (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China). EPICSXL software was used to gate and analyze for mean fluorescence intensity (MFI) of platelet events. A ratio directly associated with VASP phosphorylation state was established by determining an MFI corresponding to experimental conditions. A platelet reactivity index (PRI) was calculated according to the formula: $PRI = [(MFI(PGE_1) - MFI(PGE_1) + ADP)/MFI(PGE_1)] \times 100$. The intra- and inter-assay coefficient of variation (CV) was < 5% and < 8%, respectively.

The HPR rates in the two DAPT groups were also compared. HPR was defined as these situations in which a 5 μmol/L ADP maximum platelet aggregation was ≥ 46%[5], or VASP results was > 50% PRI[22].

2.4 Statistical analysis

SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used to analyze the dada statistically. For continuous variables, the results were showed as mean ± standard deviation (SD) if in a normal distribution or as median and interquartile range (IQR, percentiles 25–75) if skewed distributed. Statistical significance was assessed by independent-samples *t*-test, one-way analysis of variance (ANOVA), or the Mann-Whitney U test. Chi-square or Fisher exact tests C were used for categorical variables and expressed as number, n (proportions, %). Bivariate correlation analysis was assessed with Pearson's or Spearman's correlation analysis. To identify the independent associations between MPV and HPR adjusted for hypertension, dyslipidemia, diabetes, previous PCI, angiotensin converting enzyme inhibitor (ACEI), β-blocker, LDL-C, hsCRP, and AST, multivariate logistic regression analysis was performed. And receiver-operating characteristic (ROC) curves were assessed to evaluate the predictive value of MPV for HPR. The optimal cut-off value was determined by Youden's index (YI) calculated as (sensitivity + specificity − 1). A 2-tailed *P*-value < 0.05 indicating statistical significance.

3. Results

3.1 Study population and baseline characteristics

In total, 112 consecutive participants were enrolled in this study. Table 1 showed the baseline characteristics of the two DAPT groups. It presented no significant difference in mean age, BMI and proportion of males between the two groups. The patients receiving traditional therapy had higher LVEF, more history of hypertension and less history of diabetes. The patients treated with the new therapy had more previous PCI and myocardial infarction (MI) and more frequent use of ACEI. In the laboratory data acquired after PCI, the levels of hsCRP, ALT and AST were markedly higher in the group given the new therapy. Interestingly, patients in the traditional therapy group had a significantly higher value of MPV (11.4 ± 1.4 vs 10.2 ± 0.9 fl, P < 0.001). Nevertheless, no significant difference was found in PLT count between the two groups.

Table 1
Demographics of the study population.

Variables	Traditional therapy group (n = 46)	New therapy group (n = 66)	*P*
Age, yrs.	58.1 ± 9.1	56.3 ± 11.6	0.401
Male, n (%)	36(78.3)	55(83.3)	0.499
BMI, kg/m^2	25.9 ± 3.3	25.9 ± 3.2	0.963
LVEF, %	63.0(60.0, 66.0)	60.0(52.8, 65.0)	< 0.001
Risk factors			
Hypertension, n (%)	33(71.7)	31(47.0)	0.009
Diabetes, n (%)	9(19.6)	26(39.4)	0.026
Hyperlipidemia, n (%)	43(93.5)	58(89.2)	0.441
Past history			
Previous PCI, n (%)	9(19.6)	28(42.4)	0.011
Previous MI, n (%)	17(37.0)	56(84.8)	< 0.001
Previous stroke, n (%)	10(22.2)	4(6.1)	0.012
Medications			
Statins, n (%)	46(100.0)	66(100.0)	1.000
ACEI, n (%)	11(24.4)	29(46.0)	0.022
ARB, n (%)	8(18.2)	7(11.1)	0.300
β-blocker, n (%)	38(84.4)	60(93.8)	0.112
Laboratory			
Hemoglobin, g/L	147.7 ± 14.0	143.5 ± 12.4	0.095
LDL-C, mmol/L	2.0(1.7, 2.8)	2.2(1.5, 2.7)	0.708
HsCRP, mg/L	1.1(0.5, 3.0)	2.6(1.2, 7.2)	0.006

Values are mean ± SD if the distribution is normal; median (interquartile range) if skewed; number, n (proportions, %) for categorical variables.

ACEI: angiotensin converting enzyme inhibitor; ALT: alanine transaminase; AST: aspartate transaminase; ARB: angiotensin receptor blocker; BMI: body mass index; CABG, coronary artery bypass graft; hsCRP: highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI, myocardial infarction; MPV, mean platelet volume; PCI, percutaneous coronary intervention.

Variables	Traditional therapy group (n = 46)	New therapy group (n = 66)	*P*
AST, U/L	22.0(19.0, 27.5)	27.0(20.0, 85.0)	0.007
ALT, U/L	27.0(17.0, 39.2)	32.5(22.8, 52.5)	0.022
Platelet, 10^9 cells/L	223.1 ± 60.2	244.7 ± 69.7	0.091
MPV, fl	11.4 ± 1.4	10.2 ± 0.9	< 0.001
Values are mean ± SD if the distribution is normal; median (interquartile range) if skewed; number, n (proportions, %) for categorical variables.			
ACEI: angiotensin converting enzyme inhibitor; ALT: alanine transaminase; AST: aspartate transaminase; ARB: angiotensin receptor blocker; BMI: body mass index; CABG, coronary artery bypass graft; hsCRP: highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI, myocardial infarction; MPV, mean platelet volume; PCI, percutaneous coronary intervention.			

3.2 Platelet function testing in patients of the two DAPT groups

As measured by LTA, the value of platelet aggregation induced by ADP in the traditional therapy group was dramatically higher than that in the new therapy group (38.8 ± 16.2% vs 18.5 ± 9.5%, P < 0.001; Fig. 1A). According to the results of VASP test, the new therapy group presented a significantly lower PRI level than the traditional therapy group (23.9 ± 15.9% vs 63.5 ± 21.5%, P < 0.001; Fig. 1B).

Using the criteria which has been reported in the literature[11, 23], the HPR rates were compared between the different DAPT groups and platelet function results (Fig. 2). In LTA assay, the HPR rate differed significantly between the two groups (traditional therapy: new therapy = 21.7:1.5, P < 0.001; Fig. 2A). Similar results could also be observed in the VASP assay, with a higher HPR rate in those given the traditional therapy was observed (traditional therapy: new therapy = 73.9:7.6, P < 0.001; Fig. 2B).

In addition, as shown in Additional file 2 (Fig. S2), a significant positive correlation was observed between the results for LTA and VASP assay (r = 0.660, P < 0.001).

3.3 Association between mean platelet volume and high on-treatment platelet reactivity

To investigate whether MPV could indicate the level of HPR in patients receiving DAPT, the participants were divided into three groups, according to MPV tertiles (< 10.0 fl; 10.0–11.0 fl; ≥ 11.0 fl). Table 2 shows the main clinical characteristics and biochemistry results according to the MPV values. Larger platelets were associated with higher LVEF (P = 0.026), higher Hb (P = 0.011), lower AST levels (P = 0.010) and lower PLT count (P = 0.001), and with less history of previous MI (P = 0.031). Notably, more patients in the highest MPV tertile received the traditional therapy (P < 0.001). With regard to the platelet function results,

ADP-mediated platelet aggregation ($P = 0.006$) and PRI ($P < 0.001$) was much higher in patients of the highest MPV tertile. A higher percentage of HPR was observed at VASP assay in patients with higher MPV ($P < 0.001$), and this was also true for ADP-induced aggregation at LTA test ($P = 0.048$). Furthermore, analysis showed that there existed a positive correlation between MPV levels and PRI ($r = 0.488$, $P < 0.001$), as well as ADP-mediated platelet aggregation ($r = 0.343$, $P < 0.001$) (Fig. 3).

Table 2
Clinical characteristics and chemistry results according to mean platelet volume.

Variables	I tert	II tert	III tert	*P*
	< 10.0 fl	10.0–11.0 fl	≥ 11.0 fl	
	(n = 37)	(n = 42)	(n = 33)	
Age, yrs.	58.2 ± 10.3	55.7 ± 12.1	57.4 ± 9.2	0.566
Male, n (%)	33(89.2)	31(73.8)	27(81.8)	0.216
BMI, kg/m^2	26.1 ± 3.5	25.9 ± 3.4	25.5 ± 2.6	0.758
LVEF, %	60.0(53.0, 65.0)	63.0(60.0, 65.0)	65.0(58.0, 68.0)	0.026
Risk factors				
Hypertension, n (%)	20(54.1)	20(47.6)	24(72.7)	0.083
Diabetes, n (%)	14(37.8)	14(33.3)	7(21.2)	0.304
Hyperlipidemia, n (%)	34(91.9)	38 (90.5)	29(87.9)	0.850
Past history				
Previous PCI, n (%)	15(40.5)	12(28.6)	10(30.3)	0.489
Previous MI, n (%)	29(78.4)	28(66.7)	16(48.5)	0.031
Previous stroke, n (%)	4(10.8)	4(9.5)	6(18.2)	0.494
Medications				
Statins, n (%)	37(100.0)	42(100.0)	33(100.0)	1.000
ACEI, n (%)	17(45.9)	14(33.3)	9(27.3)	0.245
ARB, n (%)	6(16.2)	3(7.1)	6(18.2)	0.313
β-blocker, n (%)	36(97.3)	34(81.0)	28(84.8)	0.078
Laboratory				
Hemoglobin, g/L	140.0 ± 13.0	147.0 ± 13.2	148.8 ± 11.9	0.011
LDL-C, mmol/L	2.4(1.7, 2.8)	2.2(1.6, 2.8)	2.0(1.7, 2.2)	0.457
HsCRP, mg/L	3.1(1.2, 8.4)	1.8(0.9, 4.7)	1.5(0.5, 6.7)	0.232
AST, U/L	25.0(20.5, 85.0)	25.5(20.8, 38.2)	21.0(16.5, 28.0)	0.010

Values are mean ± SD if the distribution is normal; median (interquartile range) if skewed; number, n (proportions, %) for categorical variables.

ADP, adenosine diphosphate; HPR, high on-treatment platelet reactivity; PRI, platelet response index. Others were as Table S1.

Variables	I tert < 10.0 fl (n = 37)	II tert 10.0–11.0 fl (n = 42)	III tert ≥ 11.0 fl (n = 33)	*P*
ALT, U/L	26.0(22.0, 42.5)	32.0(21.5, 52.0)	29.0(17.0, 40.0)	0.474
Platelet, 10^9 cells/L	257.3 ± 73.4	243.9 ± 63.2	201.4 ± 48.3	0.001
ADP aggregation, %	17.0(12.4, 25.7)	20.6(12.1, 36.5)	32.0(16.4, 51.5)	0.006
PRI, %	21(11.5, 28.0)	31.0(23.0, 66.5)	61.0(30.5, 79.0)	< 0.001
Percentage of HPR-LTA, %	0(0)	6(14.3)	5(15.2)	0.049
Percentage of HPR-VASP, %	4(10.8)	15(35.7)	20(60.6)	< 0.001
Dual antiplatelet therapy				
Traditional therapy, n (%)	6(16.2)	18(42.9)	22(66.7)	< 0.001
New therapy, n (%)	31(83.8)	24(57.1)	11(33.3)	< 0.001
Values are mean ± SD if the distribution is normal; median (interquartile range) if skewed; number, n (proportions, %) for categorical variables.				
ADP, adenosine diphosphate; HPR, high on-treatment platelet reactivity; PRI, platelet response index. Others were as Table S1.				

As can be seen in Table 3, the independence of MPV and MPV tertiles in predicting HPR at VASP assay was subsequently determined using univariate and multivariable logistic regression analysis. Results indicated that there were independently association between MPV levels and the increased prevalence of HPR at VASP assay, as well as MPV tertiles. After adjustment for percutaneous coronary intervention, previous of stroke, dual antiplatelet therapy, left ventricular ejection fraction and aspartate transaminase, MPV was significantly and independently associated with HPR (OR = 2.105, 95% CI:1.175–3.771, P = 0.012). Nevertheless, MPV and MPV tertiles did not present significant independence in predicting HPR at LTA testing. In addition, analysis of ROC curves showed a potent ability of MPV in predicting the presence of HPR at VASP assay in patients undergoing PCI and receiving DAPT (area under curve [AUC] = 0.788, 95% CI: 0.701–0.875, P < 0.001) (Fig. 4). The cut-off value of MPV in predicting HPR was 10.55 fl.

Table 3

Regression analysis to assess HPR according to MPV and MPV tertiles.[a]

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
MPV	2.797(1.813, 4.313)	< 0.001	2.105(1.175, 3.771)	0.012
MPV tertiles tertiles				
Tertile 1	1		1	
Tertile 2	4.583(1.361, 15.440)	0.014	3.537(0.644, 19.442)	0.146
Tertile 3	12.692(3.634, 44.333)	< 0.001	5.446(0.936, 31.690)	0.059

[a] Adjusted for previous of percutaneous coronary intervention, previous of stroke, dual antiplatelet therapy, left ventricular ejection fraction, and aspartate transaminase.

HPR, high on-treatment platelet reactivity; MPV, mean platelet volume.

Finally, Fig. 5 displays the MPV levels of the two groups given traditional therapy and the new therapy. It was found that the levels of MPV were significantly higher in those patients given traditional therapy than those given the new therapy ($P < 0.001$), which was also shown in Table 1.

4. Discussion

Our study, for the first time, characterized the effects of clopidogrel and ticagrelor on platelet function, using LTA and VASP assay, in a Chinese population undergoing PCI. This study first provide evidence that MPV is independently associated with HPR at VASP assay and could also be used to evaluate the platelet reactivity of patients receiving clopidogrel or ticagrelor. The three major findings in this study are as follows. (1) The effect of ticagrelor on platelet reactivity was significantly greater than that of clopidogrel, with a more potent inhibition of platelet activity measured by LTA and VASP assay. (2) ACS patients undergoing PCI who were received standard-of-care treatment with ticagrelor, on a basis of aspirin, had a lower prevalence of HPR when compared with those given clopidogrel. (3) MPV can independently indicate HPR in patients at VASP assay and was much higher in patients using clopidogrel, which potentially reflects a higher prevalence of HPR.

Many studies have previously assessed the pharmacodynamic effects of clopidogrel and ticagrelor in patients with ST-segment elevation myocardial infarction (STEMI) undergoing early PCI using different PFTs, and have reported that ticagrelor provided more potent and prompt platelet inhibition than clopidogrel[24]. In particular, several clinical trials demonstrated that the primary efficacy end point and clinical benefits favored ticagrelor compared with clopidogrel in ACS patients; the former markedly reduced the mortality due to stroke, vascular causes, and myocardial infarction[25, 26]. In this study, the effect on platelet function of ticagrelor and clopidogrel in Chinese patients agreed with the findings

reported in Western populations. Although there have been several studies investigating the pharmacology and bleeding risk associated with two anti-platelet drugs among Asian populations[27, 28], few studies have concentrated on their effects on platelet function in such populations.

Various kinds of PFTs have been applied to monitor platelet activity in the setting of DAPT (aspirin and clopidogrel or ticagrelor) in large clinical trials. Verify Now, LTA, MEA and flow cytometry are most intensively used among those techniques. LTA as a traditional technique has always been acknowledged as the most classical method. VASP phosphorylation measures activation-dependent platelet signaling. This assay required small sample volumes and the whole blood, maintaining high stability and dependent on the P2Y12 receptor, the site of action for clopidogrel and ticagrelor[29]. Therefore, VASP assay was used in many clinical trials on the background of the above characteristics. Meanwhile, it has shown a pretty good correlation with LTA results, which was also seen in our results in Fig. S2. In our study, we used LTA and VASP assay and has found evidence for a significant effect of ticagrelor on platelet inhibition. In addition, use of LTA and VASP testing may identify patients who are at high risk of thrombotic events like cardiac death and stent thrombosis during follow up[30]. Furthermore, a higher HPR rate in patients receiving clopidogrel was observed in our study. This finding indicated that clopidogrel was more prone to induce drug resistance in Chinese individuals. This could guide a more efficient tailored therapy for those patients who were identified as very high risk.

Further, we provided evidence that MPV, which has been proposed as a cheap and easy-to-obtain marker of platelet size, could indicate platelet reactivity and the level of HPR in patients receiving DAPT. A close relationship has been demonstrated between MPV and cardiovascular risk factors including obesity, diabetes mellitus, hypertension, hypercholesterolemia and other factors[31, 32]. However, data relating MPV with acute coronary and cerebrovascular events are still contrasting. Lippi et al.[33] demonstrated that there was a significantly increase of MPV levels in ACS patients than that in non-ACS patients. And platelet size could predict impaired angiographic reperfusion and the death rate in STEMI patients undergoing PCI[34]. Contrastingly, Tavil et al. demonstrated that MPV was related to central obesity, hypertension and hypercholesterolemia, but not to coronary artery disease (CAD), in patients referred for coronary angiography[35]. The role of MPV in indicating the response to antiplatelet drugs has also raised great debate. Asher et al.[36] documented a higher rate of HPR with larger platelets after clopidogrel loading dose received by patients with acute myocardial infarction. Kubica et al.[37] has also reported similar findings in patients undergoing PCI. In addition, larger-sized platelets could independently predict the risk of high residual platelet reactivity for the treatment of aspirin + clopidogrel, also in patients treated with PCI[38]. However, Monica et al.[19] found no impact of larger platelet volume on the majority of platelet function tests, and in particular on ADP-mediated aggregation or the response to clopidogrel or ticagrelor. Our present study evaluated the role and effect of MPV on platelet function in patients with DAPT and confirmed the well-established strict association of MPV with other platelet function parameters, including ADP-induced aggregation conducted by LTA and PRI in the VASP assay. Regarding the variation in the role of MPV in indicating platelet function, it has been considered that this may be related to the various PFTs used in different studies. We found that MPV was related to HPR only at the VASP test but not at the LTA assay. Similar results for the association between MPV and HPR could be

found at MEA test, according to Kim et al.[38]. Of note, it presented a very low correlation between the results in MEA test and platelet volume indices, although there was a strong correlation between VASP test parameters and MPV. It could be noted that there was a significant difference in the baseline value of MPV in the two treatment arms. To avoid drawing conclusion on MPV questionable, the dual antiplatelet therapy was added into multivariate regression analysis to assess the independence of MPV and MPV tertiles in predicting HPR. Therefore, results obtained could be rational and the conclusion we made could also be reasonable.

It has been demonstrated that ticagrelor had superiority over clopidogrel in suppressing platelet function in ACS patients, with a more pronounced antiplatelet effect during the initial treatment phase and during maintenance therapy[39]. Our present study is consistent with previous research. Recently, the EROSION study[40] reported that DAPT with aspirin and ticagrelor without stenting may be an option for patients with ACS caused by plaque erosion. Therefore, the potential clinical application of ticagrelor in anti-thrombotic therapy for ACS patients should not be ignored.

In this study, several limitations about its design should be stated. Firstly, the absence of long-term follow-up of our patients should be considered, and, therefore, we cannot evaluate the impact of the two different DAPT treatment on clinical outcome. Furthermore, we need to enlarge the dataset in order to improve the representativeness and reliability of results. In addition, genetic factors' impact was not evaluated in this study, such as CYP2C19 polymorphism, on anti-platelet drug responsiveness; the response to clopidogrel is closely associated with the polymorphism of CYP2C19. The results of this study may therefore have been confounded by the prevalence of CYP2C19 polymorphism.

5. Conclusions

Our study investigated the antiplatelet effect of clopidogrel and ticagrelor in Chinese patients undergoing PCI, using two platelet function test, LTA and VASP assay. Ticagrelor has markedly greater antiplatelet effect than clopidogrel, with a superiority in inhibiting platelet activity and a lower HPR rate. In addition, an independent association between MPV and high HPR prevalence at VASP assay was found. Clinicians should be aware that MPV could be another potential marker to reflect the platelet reactivity in response to anti-platelet drugs and take it into consideration during antiplatelet therapy.

List Of Abbreviations

ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndromes; ADP, adenosine diphosphate; ALT, alanine transaminase; ANOVA, one-way analysis of variance; AST, aspartate transaminase; BMI, mass index; CAD, coronary artery disease; CV, coefficient of variation; DAPT, dual antiplatelet therapy; Hb, hemoglobin; HPR, high on-treatment platelet reactivity; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; LTA, light-transmission aggregometry; LVEF, left ventricular ejection fraction; MEA, multiple electrode platelet aggregometry; MFI, mean fluorescence intensity; MI, myocardial infarction; MPV, mean platelet volume; PCI, percutaneous

coronary intervention; PFA, platelet function analyzer; PFT, platelet function test; $PGE_{1,}$ prostaglandin E_1; PLT, platelet count; PRI, platelet reactivity index; ROC, receiver-operating characteristic; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TEG, thromboelastography; VASP, vasodilator-stimulated phosphoprotein; YI, Youden's index.

Declarations

- ## Ethics approval and consent to participate

The study protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the College of Medicine Research Ethics Committee, Fuwai Hospital. Written informed consent was obtained from individual.

- ## Consent for publication

Not applicable.

- ## Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to subsequent researches based on this data base not be published but are available from the corresponding author on reasonable request.

- ## Competing interests

The authors declare that they have no competing interests.

- ## Funding

Not applicable.

- ## Authors' contributions

YZ was key in the design of the work and had major input in writing the manuscript. RP was a major contributor for the clinical work and drafted the manuscript. XJL and GWC provided technical contributions in platelet function tests. XMW and JXY helped in screening patients and detecting of laboratory data. MXH provided technical suggestions and supervised the study. XC and ZZ supervised the study, supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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41. **Additional files**:.
42. **Additional file 1.pdf: Fig. S1.** Study flow diagram.
43. **Additional file 2.pdf: Fig. S2.** Relationships between the results obtained by light transmittance aggregometry (LTA, %) and vasodilator-stimulated phosphoprotein (VASP) (PRI, %) assay systems post-percutaneous coronary intervention (PCI). Correlation coefficient (r) was calculated using Pearson's method.

Figures

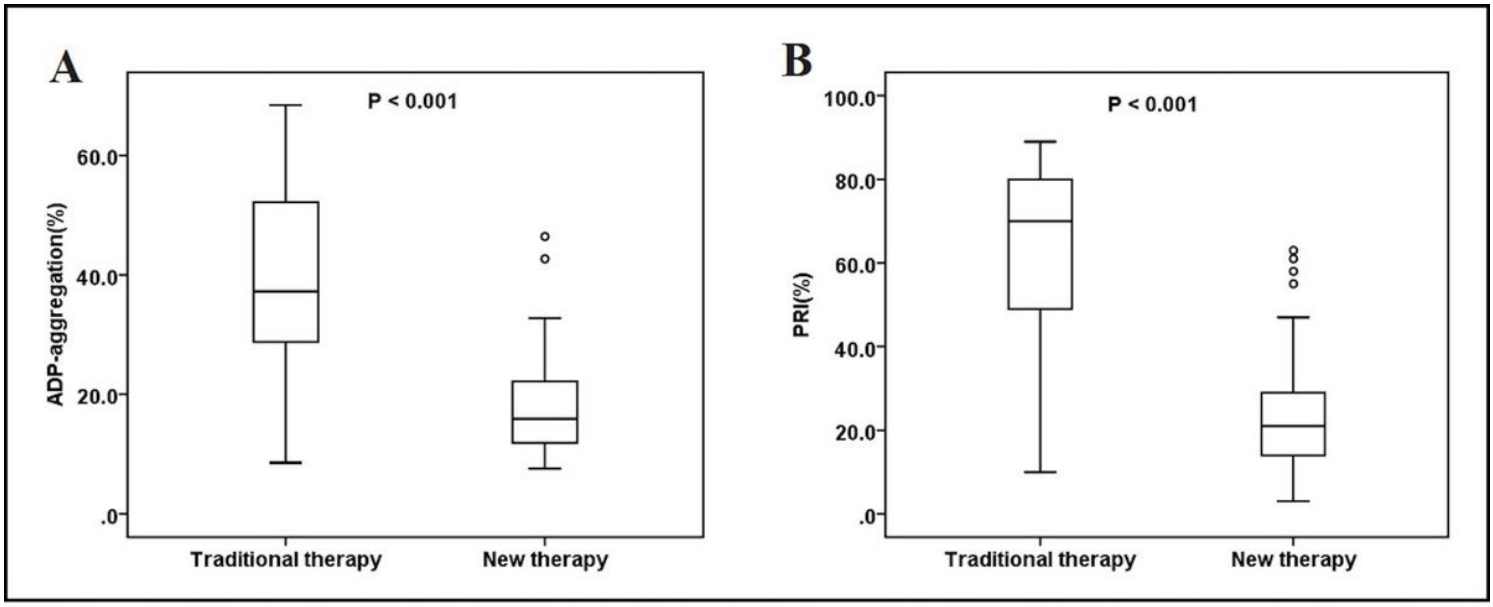

Figure 1

The platelet function test values for different devices, measured post-percutaneous coronary intervention (PCI). (A) Light transmittance aggregometry (ADP-aggregation, %); (B) Vasodilator - stimulated phosphoprotein test (PRI, %). Error bars indicate SD. Abbreviations: ADP, adenosine diphosphate; PRI, platelet response index.

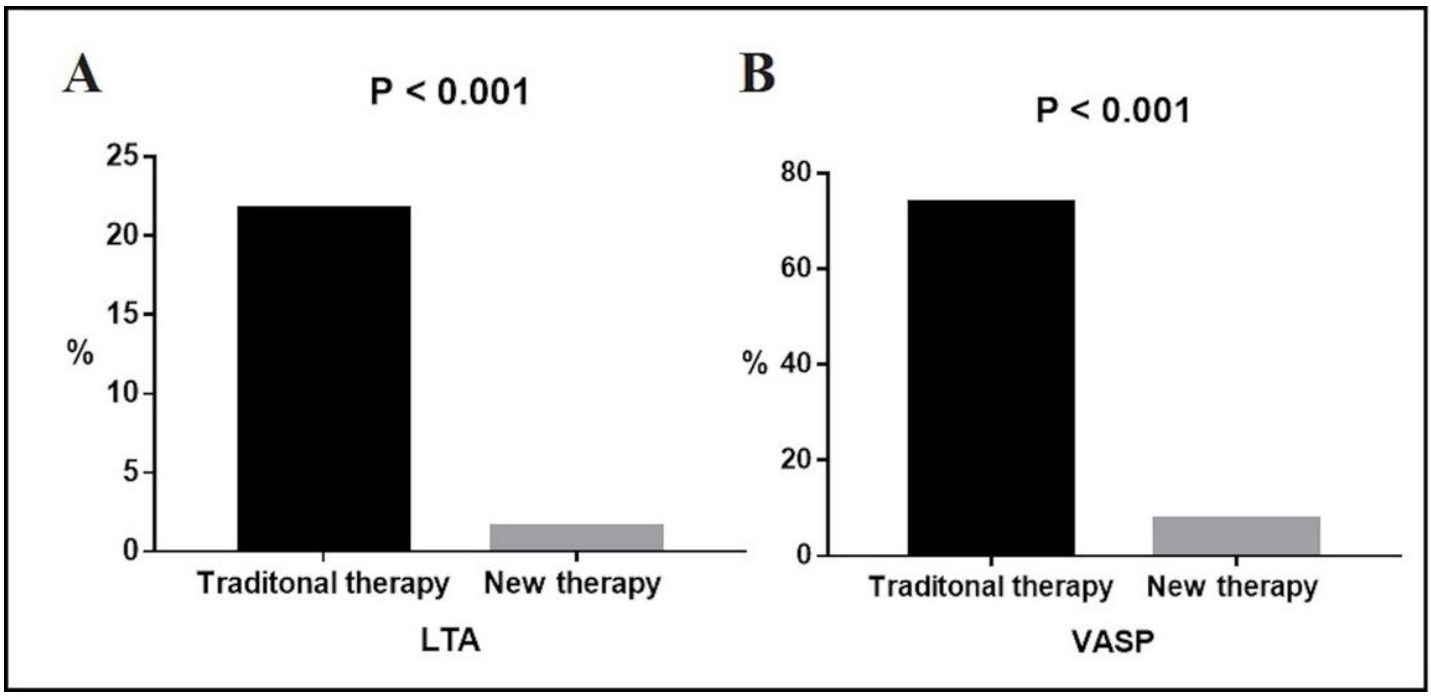

Figure 2

The percentage of high platelet reactivity (HPR) measured post-percutaneous coronary intervention (PCI) in different groups. (A) ADP-Light transmittance aggregometry (LTA); (B) Vasodilator-stimulated phosphoprotein (VASP) test.

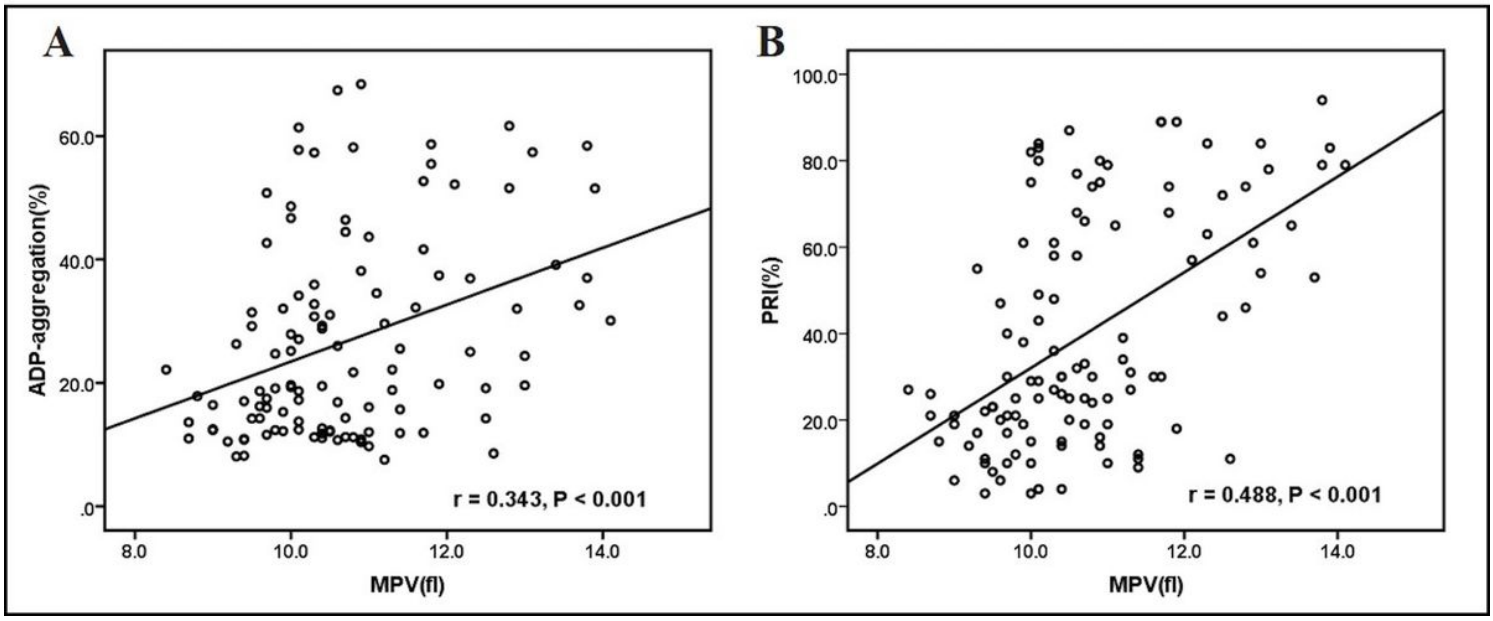

Figure 3

Relationships between mean platelet volume (MPV) and platelet aggregation results. (A) LTA after adenosine-diphosphate stimulation; (B) VASP test. Correlation coefficient (r) was calculated using Pearson's method.

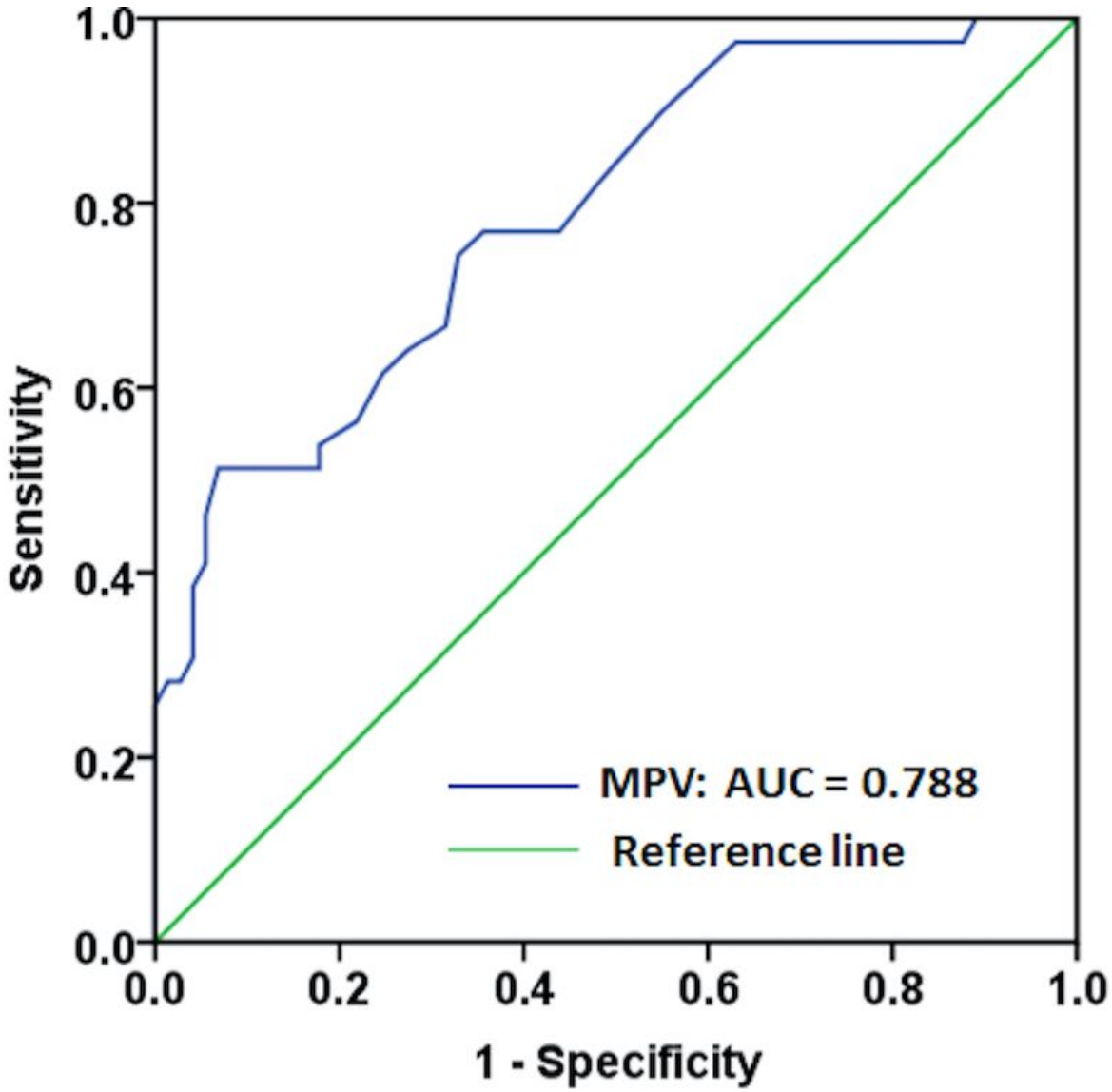

Figure 4

Receiver operating characteristic (ROC) curve of MPV for predicting HPR at VASP assay.

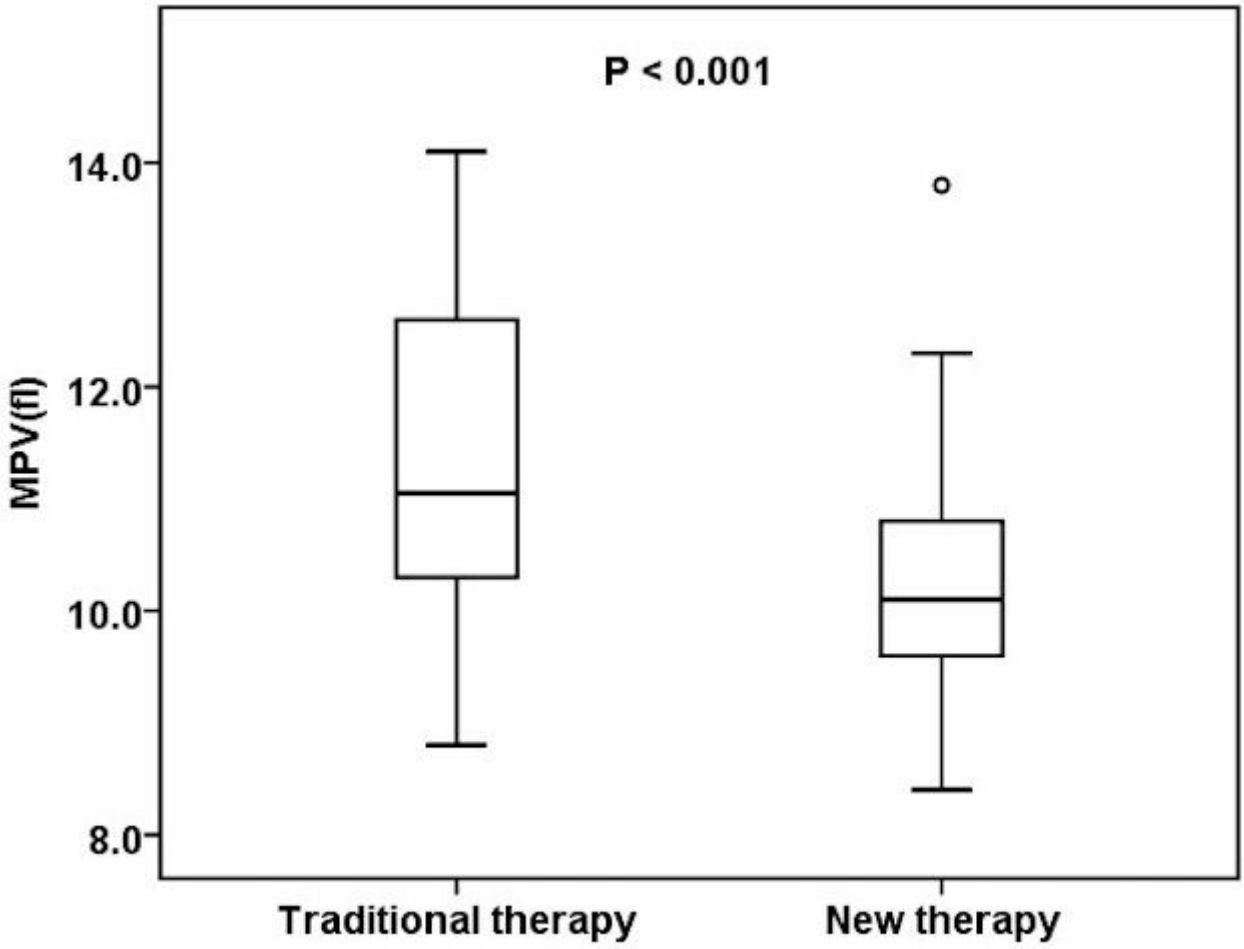

Figure 5

The comparison of MPV levels in the groups given traditional therapy and new therapy.

Supplementary Files

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