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ORIGINAL RESEARCH ARTICLE

Effect of clopidogrel gene on platelet reactivity and major cardiovascular events in patients with acute coronary syndrome

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ABSTRACT

Objective To investigate the effect of clopidogrel gene polymorphism on platelet reactivity and major cardiovascular events in patients with acute coronary syndrome (ACS). Methods 149 patients with ACS who underwent percutaneous coronary intervention (PCI) in Zhongshan Hospital Affiliated to Fudan University from January to December 2019 were included. All patients were tested for clopidogrel related genotypes after admission. Aspirin (100mg/d) and clopidogrel (75mg/d) were taken regularly after operation, and the inhibition rate of platelet aggregation (IPA) induced by adenosine diphosphate (ADP) was detected. According to the IPA results, the patients were divided into two groups: high platelet reactivity (HPR) group after clopidogrel treatment (IPA<30%) and low platelet reactivity (LPR) group after clopidogrel treatment (IPA>30%). Results: according to IPA results, there were 23 cases (15.44%) in HRP group and 126 cases (84.56%) in LRP group. The IPA induced by arachidonic acid (AA) in HRP group was significantly lower than that in LPR group (P <005). There were significant differences in CYP2C19*2, CYP2C19* 3, ABCB1 AND PON1Q192R loss of function (LOF) alleles between the two groups (p<005). Multivariate logistic regression analysis showed that CYP2C19 * 2DF allele was associated with mace after PCI (or= 3112, 95% C I 1048~9241, P = 0041). Conclusion: clopidogrel gene polymorphism has certain effect on platelet reactivity in patients with ACS. CYP2C19 * 2 gene mutation is related to mace after PCI.

Keywords*:* acute coronary syndrome; clopidogrel; gene polymorphism; platelet reactivity; major adverse cardiovascular events

Acute coronary syndrome (ACS) is a serious type of coronary heart disease, which is usually caused by rupture of coronary atherosclerotic plaque, reduction of blood flow and thrombosis [1]. According to the guideline recommendations [2-3], aspirin and clopidogrel combined antiplatelet therapy can prevent major adverse cardiovascular events (MACE) in patients with ACS after percutaneous coronary intervention (PCI) stent implantation. However, studies have reported that 5% ~15% of ACS patients have clinical end points such as myocardial infarction, stroke and even death, which is mainly due to the difference of individual response to clopidogrel [4]. Clopidogrel is an inactive precursor drug, which is absorbed through the intestine. In vivo, it needs to be converted into active metabolites by

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liver cytochrome P450 (CYP450) enzymes, and then binds to adenosine diphosphate (ADP) receptor P2Y12 coupled with adenylate cyclase on the surface of platelets to selectively inhibit platelet aggregation [5]. Among them, CYP2C19 in CYP450 enzyme system is the main gene that affects the efficacy of clopidogrel. Studies have shown that the decreased function of CYP2C19 alleles (*2/*2, *2/*3, *3/*3) may be related to the increased risk of stent thrombosis and mace [6-7], and the slowing down of clopidogrel metabolism caused by CYP2C19 alleles has also been proved to reduce the anti platelet activity of load dose clopidogrel in ACS patients [8]. Other studies have found that efflux pump P-glycoprotein (P-gp) transports drugs through the extracellular membrane and intracellular membrane encoded by ABCB1, which may lead to the variability of clopidogrel response by affecting absorption [9]. In addition, paraoxonase 1 (PON1) in the coding gene participates in the hydrolysis reaction during clopidogrel activation, so its gene polymorphism also affects the biological activation of clopidogrel [10]. The purpose of this study was to investigate the relationship between clopidogrel related metabolic gene polymorphism and its clinical antiplatelet effect and mace in patients with ACS.

1. Data and methods

1.1. General information

Inclusion and exclusion criteria

Inclusion criteria: (1) patients with ACS, including acute ST segment elevation myocardial infarction, non ST segment elevation myocardial infarction and unstable angina pectoris; (2) Older than or equal to 18 years old; (3) Receiving aspirin and clopidogrel dual antiplatelet therapy; (4) Chest pain was greater than or equal to 10 minutes, ST segment and T wave of ECG were changed, and cardiac biomarkers were increased. Exclusion criteria: (1) patients who were allergic or contraindicated to aspirin or clopidogrel; (2) Younger than 18 years old or without informed consent; (3) History of bleeding and hemorrhagic disease; (4) Severe hepatic or renal insufficiency; (5) Cilostazol or glycoprotein ii b/ iii a receptor antagonists were also used.

General information

The clinical data of 170 patients with ACS diagnosed in the cardiac intensive care unit of our hospital from January to December 2019 were collected. All patients presented with chest pain, discomfort, shortness of breath, dizziness, nausea, sweating and other symptoms, accompanied by elevated cardiac biomarkers troponin and creatine kinase levels, and ECG T wave and ST segment changes. All patients underwent PCI. This study was reviewed and approved by the ethics committee of our hospital, and all patients signed written informed consent.

1.2. Method

Treatment method. All patients were given clopidogrel (300 mg) and aspirin (300 mg) before PCI, and then maintained 75 mg/d clopidogrel combined with 100 mg/d aspirin antiplatelet therapy. All patients received low molecular weight heparin, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor antagonist (ARB), statins β Receptor blockers, proton pump inhibitors (PPI) and nitrates.

Gene detection. After admission, about 2 ml of whole blood samples were collected and placed in a vacuum collector containing the anticoagulant ethylenediaminetetraacetic acid (EDTA) for clopidogrel gene detection. Qiaamp blood DNA Extraction Kit (German Qiagen company) was used to separate the DNA of each patient, and the single nucleotide polymorphism (SNP) of the gene was detected based on the sequence mass array platform. Cyp2c19*2, CYP2C19*3, ABCB1 and PON1 Q192R lof genes were point mutations of 681g> a (rs4244285), 636g > A (rs4986893), 3435c>t (rs1045642) and 575a>g (rs662), respectively. According to the different pharmacokinetic

characteristics of clopidogrel encoded by enzymes of different genotypes, the wild genotype (*1/*1) is classified as fast metabolic type (EM), the mutant heterozygous genotype (*1/*2, *1/*3) is classified as intermediate metabolic type (IM), and the mutant homozygous genotype (*2/*2, *2/*3, *3/*3) is classified as slow metabolic type (PM) [11].

Determination of platelet aggregation inhibition rate. Five days after the loading dose of clopidogrel was administered, about 4 ml of whole blood samples were collected, the platelet aggregation inhibition rate (IPA) was measured by the thromboelastography analyzer (TEG, heomescope company of the United States), and the amplitude changes were recorded by computer. The maximum change in coagulation intensity amplitude is defined as the maximum coagulation intensity (MA). According to different blood sample inducers, Ma can be divided into the maximum coagulation intensity $(MA_{Thrombin})$ induced by thrombin and 20 μ mol/ladp induced maximal coagulation intensity (MA_{ADP}) and fibrinogen induced (MA_{Fibrin}) maximal coagulation intensity. ADP $IPA(\%) = (MA_{ADP} - MAFibrin) / (MA_{Thrombin} - MA_{Fibrin}) \times 100\%$ induced, $IPA < 30\%$ including high platelet reactivity (HPR) group after clopidogrel $IPA \geq 30\%$ treatment and low platelet reactivity (LPR) group after clopidogrel treatment [12]. At the same time, arachidonic acid (AA) $IPA < 50\%$ induced was defined as aspirin resistance.

Follow up and clinical end points

All patients were followed up by regular outpatient service and telephone within 12 months after PCI. The incidence of mace in follow-up patients was mainly observed, including cardiac death, cardiovascular mortality, myocardial infarction, ischemic stroke and revascularization of diseased vessels.

Table 1. Clinical characteristics of patients with ACS (*n*=149)

Clinical features	$\bar{x} \pm s$ /[n(%)]
Age ($\bar{x} \pm s$, years)	65.29±11.23
Male [*n*(%)]	118(919)
Body mass index(BMI)($\bar{x} \pm s$, kg/m^2)	24.36±3.14
Smoking history [*n*(%)]	79(53.02)
Drinking history [*n*(%)]	30(20.13)
Family history [*n*(%)]	4(2.68)
Complications [*n*(%)]	
Hypertension	100(67.11)
Local blood lipids	12(8.05)
Diabetes	51(34.23)
Previous history of coronary heart disease [*n*(%)]	
Miocardial infarction	27(18.12)
PCI	27(18.12)
Coronary bypass	4(2.68)
Combined medication [*n*(%)]	
Statins	148(933)
β Receptor blocker	137(1.95)
ACEI or ARB	122(81.88)
PPI	132(88.59)
Nitrates	120(80.54)
MACE[*n*(%)]	
Revascularization	21(14.09)
Ischemic stroke	3(2.01)

1.3. Statistical treatment

All data were analyzed by spss23.0 software. Continuous variables are $\bar{x} \pm s$ expressed in and classified variables are expressed in rates. Hardy Weinberg equilibrium test χ^2 uses test. The single factor analysis of HPR used independent sample t-test χ^2 and test. Multivariate analysis of HPR and mace was performed by non conditional logistic regression. P <0.05 was statistically significant.

2. Results

2.1. Basic characteristics of patients

Among all the included patients, 21 patients were lost to follow-up. The sample size of the final study was 149, including 118 males (79.19%) and 31 females (20.81%); the average age was (65.29 ± 11.23) years. During the 12-month follow-up after

PCI, 21 patients (14.09%) were readmitted to receive revascularization, and 3 patients (2.01%) had ischemic stroke. See **Table 1**.

Table 2. Genotype distribution and allele frequency distribution of patients (n=149)

Genelocus	Frequency[*n*(%)]	MAF(%)	χ^2	*P*
CYP2C19*2		2181	195	0.3
GG(*1/*1)	94(63.09)			
GA(*7*2)	45(30.20)			
AA(*2/*2)	10(6.71)			
CYP2C19*3		4.36	0.31	0.86
GG*1/*1)	16(91.28)			
GA(*7*3)	13(8.72)			
AA(*3/*3)	0			
ABCBLC3435T	37.92	5.23	0.07	
CC	64(42.95)			
CT	57(38.26)			
TT	28(8.79)			
PON1Q192R		46.97	28.09	<0.05
AA	49(32.88)			
AG	42(28.19)			
GG	58(38.93)			

Note: MAF is the minimum allele frequency.

2.2. Genotype distribution and allele frequency distribution of patients

In this study, four genotypes related to the clinical efficacy of clopidogrel were detected, including CYP2C19*2 (rs4244285), *3 (rs4986893), ABCB1 C3435T (rs1045642) and PON1 Q192R (rs662). Except PON1 Q192R (rs662), the genetic variation of all study populations was in Hardy Weinberg equilibrium (p>0.05), as shown in **Table 2**.

2.3. Single factor analysis to predict risk factors of HPR

Among the 149 patients selected, 23 (15.44%) were in the HPR group and 126 (84.56%) were in the LPR group. Compared with the LPR group, the IPA induced by AA in the HPR group was significantly lower (P <0.05). In the presence of CYP2C19*2, CYP2C19*3, ABCB1, PON1 Q192R lof alleles, the difference between the two groups was statistically significant (p<0.05), and there was no statistical difference in other indicators Academic significance (p>0.05), see **Table 3**.

Table 3 Risk factors of HPR predicted by single factor analysis

Clinical features	HPR group (*n*=23)	LPR group (*n*=126)	P
Age ($\bar{x} \pm s$, years)	64.61±12.22	65.41±11.09	0.753
Male [*n*(%)]	15(65.22)	103(81.75)	0.073
BMI($\bar{x} \pm s$, kg/m^2)	25.67±3.20	24.11±3.09	0.121
Smoking history [*n*(%)]	9(39.13)	65(51.59)	0.272
Drinking history [*n*(%)]	3(13.04)	27(21.43)	0.571
Family history [*n*(%)]	0	4(3.17)	1.000
Complications [*n*(%)]			
Hypertension 14 (60.87)	86(68.25)	0.488	
Hyperlipidemia 1 (4.35)	11(8.73)	0.693	
Diabetes 7 (30.43)	44(34.92)	0.677	
Laboratory index ($\bar{x} \pm s$)			
Plt(× 10^9 L^{-1})	190.64±44.44	205.17±62.72	0.275
Hb(g/L)	134.26±17.98	131.86±20.71	0.603
Hct(%)	40.87±5.44	39.74±4.74	0.307
PT(s)	11.89±0.70	11.83±1.36	0.821
APTT(s)	28.38±2.87	29.29±6.16	0.491
ALT(U/L)	47.39±27.24	44.00±53.15	0.766
AST(U/L)	174.65±184.64	131.17±151.19	0.223
Egfr[ml/(min·1.73 m^2)]	76.29±25.86	81.49±22.71	0.434
LDL(x±s, mmol/L)	2.51±1.10	2.46±0.85	0.824
AA-IPA(x±s, %)	37.09±29.96	73.02±26.65 <0.001[a]	
Combined medication [*n*(%)]			
Statins 23 (100.00)	125(99.21)	1.000	
β Receptor blocker 21 (91.30)	116(92.06)	1.000	
ACEI or ARB	16(69.57)	106(84.13)	0.095
PPI	19(82.61)	113(89.68)	0.302

Nitrates 16 (69.57)	104(82.54)	0.148	
Genotype [*n*(%)]			
CYP2C19*2			
GA(*1/*2)	13(56.52)	32(25.40)	0.001[a]
AA(*2/*2)	5(21.74)	5(3.97)	0.002[a]
CYP2C19*3			
GA(*1/*3)	5(21.74)	8(6.35)	0.016[a]
ABCB1			
CT	8(34.78)	49(38.89)	0.709
TT	8(34.78)	20(15.87)	0.033[a]
PON1 Q192R			
AG	10(43.48)	32(25.40)	0.001[a]
GG	10(43.48)	48(38.10)	0.034[a]

Note: PLT is platelet count; hb is hemoglobin; HCT is hematocrit; PT is prothrombin time; APTT is the activated partial thromboplastin time; ALT is alanine aminotransferase; AST is aspartate aminotransferase; EGFR is glomerular filtration rate; LDL is low density lipoprotein; aa-ipa was the inhibition rate of platelet aggregation induced by arachidonic acid; [a]*P* <0.05.

2.4. Multivariate logistic regression analysis to predict risk factors of HPR

In univariate analysis, the variables with P <0.15 (sex, BMI, aaipa, combined ACEI or ARB, combined nitrates, genotype CYP2C19*2, CYP2C19*3, ABCB1, PON1 q192rlof) were used as covariates and HPR as dependent variables for logistic regression analysis. The results showed that aa-ipa, CYP2C19*2, CYP2C19*3lof alleles were risk factors for HPR. See **Table 4**.

Table 4. Risk factors of HPR predicted by multivariate logistic regression analysis

Clinical features	*OR*	95%CI	*P*
Male	0.394	0.077~2014	0.263
BMI	1237	0.985~1553	0.068
AA-IPA	0.953	0.928~0.97	<0.001a
Concomitant medication			
ACEI or ARB	0.274	0.061~1235	0092
Nitrates	0.347	0.086~1402	0.137
Genotype			
CYP2C19*2	7.758	2082~28.91	0.002[a]
CYP2C19*3	5.046	1023~24.895	0.047[a]
ABCB1	0.285	0.074~1090	0067
PON1Q192R	2716	0.531~13.901	0230

Note: [a]*P*<0.05.

2.5. Multivariate logistic regression analysis to predict risk factors of mace

During the 12-month follow-up, the main mace included rehospitalization due to revascularization and ischemic stroke events in 24 patients (16.11%). In multivariate logistic regression analysis, there was no significant difference between aspirin resistance (aa-ipa<50%) and adp-ipa<30% and mace (P >0.05). Cyp2c19*2lof allele was associated with high risk of mace within 12 months after PCI (or =3.112, 95%ci 1.048~9.241, P =0.041). See **Table 5**.

3. Discussion

At present, the standard dual antiplatelet therapy (aspirin combined with clopidogrel) after PCI has become the main treatment for ACS patients, which can reduce the incidence of adverse cardiovascular events. It was found that the individual difference of clopidogrel was of great significance to the platelet reactivity of patients after treatment. Routine detection of clopidogrel related genes has certain guiding significance for the individualized treatment of ACS patients. The genotypes of clopidogrel were detected in 149 ACS patients undergoing PCI, and the platelet reactivity after clopidogrel treatment was detected by thromboelastography (TEG).

Table 5. Risk factors of mace predicted by multivariate logistic regression analysis

Risk factor	MACE [*n*=24, *n*(%)]	*OR*	95%CI	*P*

>65 Years old	12(50.00)	0904	0.312~2.622	0852
Male	21(87.50)	2052	0.459~9.165	0347
BMI≥25 Kg/m^2	7(29.17)	0.491	0.166~1454	0.199
Smoking history	13(54.17)	1355	0.444~4.130	0593
Hypertension	13(54.17)	0580	0.216~1554	0278
Diabetes	6(25.00)	0723	0.244~2.145	0559
Hyperlipidemia	2(8.33)	0976	0.159~5.988	0979
AA-PA<50%	13(54.17)	2799	0.923~8.490	0069
ADP-IPA<30%	7(29.17)	1345	0.337~5.374	0675
Genotype lof				
CYP2C19 * 2	15(62.50)	3.112	1048~9.241	0.041
CYP2C19*3	3(12.50)	0872	0.177~4.309	0867
ABCB1	16(66.67)	1491	0.525~4.235	0454
PON1Q192R	18(75.00)	1162	0.382~3.534	0.791

Note: [a]*P*<0.05.

As a precursor drug, clopidogrel needs two-step oxidation reaction of cell P450 enzymes to convert into active metabolites and play its role. The enzyme protein encoded by CYP2C19 gene is the key enzyme in clopidogrel metabolism. The CYP2C19 gene polymorphism is closely related to clopidogrel resistance [13]. Studies have shown that CYP2C19 lof allele will lead to the decrease of IPA induced by ADP and increase the risk of stent thrombosis [14]. In this study, the incidence of CYP2C19*2 lof alleles was high (36.91%), but the incidence of CYP2C19*3, abcbc3435t and PON1 Q192R lof alleles were similar to previous studies. In addition, the occurrence of lof allele of PON1 Q192R (rs662) (MAF was 46.97%) was statistically significant (p<0.05), which may be related to the differences among the study population.

The occurrence of HPR is the result of multiple factors such as genetic factors, cellular factors and clinical factors, among which genetic factors gene polymorphism plays a key role. In this study, age, gender, BMI, smoking history, drinking history and cardiovascular risk factors including hypertension, hyperlipidemia and diabetes were taken as the relevant risk factors for ACS. In univariate analysis, there were significant differences in aa-ipa, CYP2C19*2, CYP2C19*3, abcb1tt and PON1 Q192R lof alleles between the two groups (P <0.05). Logistic regression analysis showed that CYP2C19*2 and CYP2C19*3 were independent risk factors for HPR.

CYP2C19 is an indispensable drug metabolizing enzyme for the biotransformation of clopidogrel. Cyp2c19*2 and CYP2C19*3 lof alleles damage biological activity, reduce the concentration of active metabolites of clopidogrel, weaken the antiplatelet effect of clopidogrel, and thus increase the risk of adverse cardiovascular events [15]. The results showed that CYP2C19*2 and CYP2C19*3 lof alleles were associated with increased platelet reactivity in ACS patients (P <0.05). PON1 is another genetic factor affecting platelet activation and plays an important role in the biotransformation of clopidogrel. Luwenqi et al. [16] have shown that PON1 (rs662) A allele in Chinese population is an independent risk factor for HPR. The results showed that the incidence of pon1q192r lof allele in HPR group was significantly higher than that in LPR group (P <0.05), and no correlation between PON1 gene polymorphism and HPR was found. In addition, the SNP change of ABCB1 will affect the absorption and metabolism of clopidogrel in the intestine, which may be one of the reasons for the low reactivity of clopidogrel. It has been reported that compared with CC type or CT type patients, clopidogrel absorption in TT type patients is reduced, which is significantly related to early thrombosis in stents [9]. In this study, the incidence of abcb1tt allele in HPR group was significantly higher than that in LPR group (P <0.05), and there was no significant difference in the incidence of CC and CT between the two groups (P >0.05).

As a classical antiplatelet drug, aspirin can not only inhibit platelet aggregation by inhibiting cyclooxygenase, but also play a role in ADP induced platelet inhibition [17]. In this study, the IPA induced by AA in HPR group was significantly lower than that in LPR group (P <0.05). In addition, the incidence of cardiovascular adverse events in patients with aspirin resistance is higher (54.17%), which may be related to the insufficient inhibition of cyclooxygenase dependent thromboxane A2 formation caused by aspirin resistance [18]. Therefore,

active dual antiplatelet therapy plays an important role in preventing thromboembolic events after PCI.

The gene polymorphism of clopidogrel is closely related to the occurrence of mace after PCI. Sun et al. [19] found that the risk of mace in patients with CYP2C19 intermediate metabolism and slow metabolism is 2.664 times higher than that in patients with fast metabolism. This is because clopidogrel can not be biotransformed by CYP2C19 lof allele, and can not effectively inhibit the activity of platelets, resulting in thrombosis. This study analyzed the risk factors of 24 patients with mace. The results showed that the CYP2C19*2 lof allele was associated with the increased incidence of mace compared with the non lof allele, indicating that the CYP2C19*2 lof allele was associated with the occurrence of mace after PCI.

This study has some limitations: (1) the sample size of the study is small, and large-scale prospective, randomized and well controlled trials are needed to evaluate the correlation between clopidogrel polymorphism and antiplatelet effect; (2) The follow-up time of patients is short, and prolonging the follow-up time may provide greater value for future research; (3) The way of follow-up needs to be optimized. Telephone follow-up may not fully show the prognosis of patients, and a more optimized follow-up plan needs to be adopted in future research; (4) The occurrence of bleeding events after PCI was not observed.

Conflict of interest

The authors declare no conflict of interest.

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