Analysis The Effect of Gene and Platelet Testing Guide Dual Anti-Upgrade Therapy After PCI in Patients With ACS

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Research Article

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Abstract

Objective

To analyze whether CYP2C19 gene and platelet testing guide ACS patients PCI benefit from postoperative dual antiplatelet escalation therapy.

Methods

Selecting ACS patients with 209 routine PCI surgery from January 2018 to January 2019 in Department of Cardiology, Third Affiliated Hospital of Guangzhou Medical University. Preoperative administration of aspirin 300mg and clopidogrel 600mg, and continued administration of clopidogrel 75mg/d and aspirin 100mg/d after operation. Genotype and light transmittance aggregation (LTA) was detected by gene chip 24 h after operation. According to genotype the remaining patients were divided into non loss of function (Non-LOF) alleles group Extensive-metabolisms (EMs) type, loss of function (LOF) alleles group as Intermediate metabolic (IMs) type and Poor-metabolisms (PMs) type. Define the maximum platelet aggregation rate (MPA)≥46% as hyperplatelet reactivity (HPR). The LOF group consisted of 23 patients who had both HPR and proclopidogrel and were upgraded to tigrillo for further treatment.The remaining patients without HPR who continued to be treated with clopidogrel comprised 90 patients in the LOF group without upgrade and 95 patients in the non-LOF group who continued to be treated with clopidogrel.Major adverse cardiovascular events (MACE) were recorded in the follow-up period of 1 year, and the incidence of MACE in the three groups was compared to determine whether gene and platelet detection could guide the benefit of dual anti-platelet upgrade therapy in ACS patients after PCI.

Results

There were 26 cases occurred during follow-up MACE, among which the incidence of unstable angina recurrence and overall MACE in the LOF allele-not-up group was the highest and significantly different compared with the Non-LOF allele group ($P<0.05$), there was no significant difference compared with the LOF allele-up group (0.05). while there was no significant difference between the Non-LOF allele and the LOF allele upgrading group ($P>0.05$).

Conclusions

Gene is an important factor in the difference of platelet reactivity and is associated with MACE. Upgraded treatments for high-risk patients screened for gene and platelet testing did not benefit.

Introduction

Patients after Percutaneous coronary intervention(PCI) surgery often require dual antiplatelet therapy Double antiplatelet therapy(DAPT) for at least 12 months[1], usually aspirin and P2Y12 receptor inhibitors such as clopidogrel, prasugrel, or ticagrelor[2]. However, factors such as environmental, clinical, and genetic variation can influence differences in antiplatelet responses and increase the risk of thromboembolism events, the stent, especially in clopidogrel[3], but not in prasugrel or ticagrelor[4]. How to select P2Y12 inhibitors, in addition to the clinical assessment of the risk of ischemia/bleeding, gene and platelet function testing has gradually provided the basis for individualized accurate treatment and has been paid more and more attention[5]. TROPICAL-ACS studies[6] and POPular Genetics studies[7] have shown that gene and platelet function testing can guide P2Y12 inhibitor downgrading in ACS patients, but there is still no evidence that clopidogrel upgrade can benefit ACS patients using gene and platelet function testing to guide clopidogrel upgrade after surgery[5].

The aim of this study was to compare the differences of major adverse cardiovascular events in ACS patients after different antiplatelet therapy PCI by comparing gene and platelet detection, and to determine whether gene and platelet detection

guide ACS patients PCI benefit from post-operative dual anti-upgrade therapy.

Materials And Methods

Study design and participants

This is a single-center, retrospective study. Selected 209 ACS patients who underwent PCI in cardiovascular internal medicine at the third affiliated hospital of guangzhou medical university, china from january 2018 to january 2019. 1 genotype was excluded for CYP2C19*1/*17 patients, and the remaining 208 were all included in the study and follow-up. Exclusion criteria included allergic to aspirin, clopidogrel, tigrilol and contrast agents; severe heart failure (grade NYHA); suffer from diseases of the blood system and severe anemia. complicated with serious diseases, such as malignant tumor, severe immune deficiency, severe liver and kidney failure, severe coagulation dysfunction, serious infectious diseases; long-term use of drugs that inhibit CYP2C19 genes (e.g. PPI drugs, cimetidine and various antibiotics or antidepressants);

CYP2C19 genes were divided into non-functional deletion genomes (Non-LOF) i.e. fast metabolic type (EMs): CYP2C19*1/*1; functional deletion genome (LOF) including middle metabolic type (1): CYP2C19*1/*2, CYP2C19*1/*3; slow metabolic type (PMs):*2/*2, CYP2C19*2/*3, and *3/*3. Then the Maximum platelet aggregation rate(MPA)≥46% was high platelet reactivity (HPR)[8, 9] was defined according to the results of platelet detection. Patients in the LOF group who had both HPR and proclopidogrel were upgraded to tigrillo for further treatment to form the LOF upgrade group. The remaining patients without HPR who continued to receive clopidogrel were grouped into the NON-LOF group and the non-Lof group who continued to receive clopidogrel. According to the results of gene and platelet function test, the patients were selected by the doctor according to the clinical situation. The upgrade was based on the DAPT guidelines for the 2017 ESC of coronary heart disease[1]. Aspirin was used to stop clopidogrel, and tigrilol (90 mg*14 tablets/box, AstraZeneca, UK) was given a load dose of 180 mg, followed by a maintenance dose of 90 mg/bid.

Detection of CYP2C19 genotype by gene chip

Fasting peripheral venous blood 3-4 mL, were collected by anticoagulant tube containing sodium citrate 24 hours after operation. The samples were first extracted by adding golden grape balls A protease treatment to the blood samples DNA, then 2μl of plasmids were added as primers and the samples were amplified by PCR amplification instrument. Then the results of CYP2C19 genotypes were obtained by software analysis based on the data.

Detection of platelet aggregation by LTA

24 hours after operation, the peripheral venous blood of fasting patients was extracted 3-4 mL, and mixed in two blood vessels containing 3.8% sodium citrate anticoagulant. The blood samples were separated from platelet-rich plasma and platelet-depleted plasma by high-speed horizontal centrifuge and set aside in a special double cup PRP hole. A bottle of 1 mL adenosine diphosphate ADP freeze-dried powder was taken. The same size solution was added and mixed with round cup magnetic stirring. Then 5 umol/L ADP were extracted as inducers to determine the aggregation rate of platelets min 1,3 and 5.

Endpoints

All patients were followed up for 1 year to record the patient's clinical data, medication status and major adverse cardiovascular events (MACE). It include cardiogenic death, relapse into unstable angina, myocardial infarction, stent stenosis or thrombosis, ischemic stroke, bleeding.

Sample size calculation and statistical analysis.

The continuous data are expressed as mean±standard deviation(), the inter-group comparison was tested by single factor analysis of variance, and the pairwise comparison by LSD-t test. The counting data were expressed as percentage, the chi-square test or Fisher exact probability test were used for the comparison between groups, and the Bonferroni test was used

for the comparison between the two groups. chi-square test was used to verify whether the genotype distribution was in accordance with the Hardy-Weinberg population genetic balance, P>0.05 indicated that the population was representative. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows (version 25; SPSS Inc., Chicago, IL), and a 2-tailed P<0.05 was considered statistically significant.

Results

1. CYP2C19 genotype distribution, grouping and Hardy-Weinberg genetic balance test

Table 1 shows the total of 209 patients were included in the follow-up study, of which 1 carrying CYP2C19*1/*17, failed to enter the subgroup. The final 208 patients entered the statistical analysis and were divided into two groups according to the genotype, and 95 Non-LOF the allele group, of which the fast metabolic type (EMs): 95 patients with CYP2C19*1/*1 (45.7%).A total of 113 LOF alleles (54.3%). These included middle metabolic type (IMs): 79 patients with CYP2C19*1/*2 (38.0%); 9 patients with CYP2C19*1/*3 (4.3%); slow metabolic type (PMs): 16 patients with CYP2C19*2/*2 (7.7%); 8 patients with CYP2C19*2/*3 (3.8%); 1 patient with CYP2C19*3/*3 (0.5%).

Table 1
CYP2C19 genotype distribution and grouping

Groups(n=208)	Metabolic pattern	Genotype	Cases	Frequency(%)
Non-LOF(n=95)	EMs(n=95)	*1/*1(636GG/681GG)	95	45.7
LOF(n=113)	IMs(n=88)	*1/ *2(636GG/681GA)	79	38.0
		*1/ *3(636GA/681GG)	9	4.3
	PMs(n=25)	*2/ *2(636GG/681AA)	16	7.7
		*2/ *3(636GA/681GA)	8	3.8
		*3/ *3(636AA/681GG)	1	0.5

Table 2 shows that according to gene distribution, statistics *2 and *3 locus gene frequency, actual genotype frequency and theoretical genotype frequency. chi-square test was used to test the actual genotype frequency and theoretical genotype frequency of *2 and *3 loci. the results showed no significant difference between actual genotype frequency and theoretical genotype frequency. P>0.05 was in accordance with Hardy-Weinberg genetic balance test, indicating that the gene frequency of this sample population was in accordance with genetic balance law and representative.

Table 2
Gene, genotype frequency and Hardy-Weinberg genetic balance test at *2 and*3 locus

Gene loci	Gene frequency (n/%)		CYP2C19 genotype actual frequency(n/%)			CYP2C19 genotype theory frequency(n/%)			X^2	*P*
	G	A	G/G	G/A	A/A	G/G	G/A	A/A		
*2	297(71.4)	119(28.6)	105(54.5)	87(41.8)	16(7.7)	106(51.0)	85(40.8)	17(8.2)	0.115	0.944
*3	397(95.4)	19 (4.6)	190(91.3)	17(8.2)	1(0.5)	189(91.0)	18(8.8)	1(0.2)	0.061	0.970

2. MPA and HPR incidence of three metabolic types

Table 3 shows the comparison between MPA three metabolic types as follows :(27.70±18.15) vs(28.96±17.13) vs(38.64±15.90), Pvs(28.96±0.020<0.05. the use of the LSD-t for a pairwise comparison suggested a significant difference

between the fast and slow metabolic types (P=0.006). MPA≥46% defined as hyperplatelet reactivity (HPR)[8, 9], a total of HPR 44 cases were detected, accounting for about 21.2% of the total. Among them ,21 cases of fast metabolism type ,18 cases of middle metabolism type and 5 cases of slow metabolism type. Use of chi-square the test was compared between groups, P=0.953>0.05, indicating that there was no significant difference in the incidence of HPR of the three metabolic types.

Table 3
Comparison of the MPA and HPR incidence among three metabolic types

Variables	EMs(n=95)	IMs(n=88)	PMs(n=25)	*P*
MPA	27.70±18.15	28.96±17.13	38.64±15.90*	0.020
HPR n(%)	21(22.1)	18(20.5)	5(20.5)	0.953
*P<0.05 compared with EMs				

3. Comparison of three groups of clinical data

Table 4 showed no significant differences in age, sex, smoking, alcohol consumption, clinical history (hypertension, diabetes, stroke, coronary heart disease), clinical diagnosis, blood examination (biochemical examination such as white blood cells, platelets, lipids and glycosylated hemoglobin) among the three groups (P>0.05), and long-term postoperative clinical use (e.g. ACEI/ARB、β receptor blockers, CCB、PPI、 statins) among the three groups (P>0.05). There was no significant difference in cardiac conditions (cardiac function (LVEF),≥3 vascular lesions and stent implantation) between the three groups (P>0.05).

Table 4
Comparison of three groups of clinical data

Variables	Total (n=208)	Non-LOF (n=95)	LOF(n=113)		*P*
			Unupgrade Group (n=90)	Upgrade Group (n=23)	
Age(years)	66.86±12.58	67.75±13.39	65.59±12.10	68.13±10.86	0.445
Male(%)	146(70.2)	64(67.4)	67(74.4)	15(65.2)	0.494
Smoking n(%)	110(52.9)	46(48.4)	49(54.4)	15(65.2)	0.324
Drinking n(%)	27(13.0)	11(11.6)	12(13.3)	4(17.4)	0.752
Clinical history n(%)					
Hypertension	130(62.5)	58(61.1)	58(64.4)	14(60.9)	0.880
DM	71(34.1)	29(30.5)	34(37.8)	8(34.8)	0.581
Stroke or TIA	22(10.6)	7(7.4)	10(11.1)	5(21.7)	0.129
CAD	37(17.8)	17(17.9)	15(16.7)	5(21.7)	0.851
Clinical diagnosis n(%)					
UA	34(16.3)	17(17.9)	14(15.6)	3(13.0)	0.822
NSTMI	66(31.7)	32(33.7)	26(28.9)	8(34.8)	0.740
STMI	108(51.9)	46(48.4)	50(55.6)	12(52.2)	0.624
Blood tests					
WBC(10^9L)	10.82±3.96	11.09±4.66	10.67±3.39	10.27±2.80	0.611
Hb(10^9L)	130.23±21.18	129.53±21.46	133.14±19.53	121.74±24.45	0.063
PLT(10^9L)	235.25±64.19	237.62±59.67	226.87±63.97	258.22±78.34	0.099
MPV(fl)	10.35±0.91	10.24±0.80	10.48±0.97	10.32±1.05	0.205
CR(umol/L)	97.59±65.45	100.61±91.19	95.53±28.14	93.13±38.78	0.821
UA(umol/L)	387.22±103.34	395.44±96.82	393.53±113.25	328.57±67.04	0.015
TC(umol/L)	4.88±1.42	4.94±1.40	4.96±1.47	4.34±1.19	0.155
TG(umol/L)	1.44±0.97	1.41±0.78	1.50±1.21	1.28±0.48	0.615
HDL-C(umol/L)	1.23±0.33	1.23±0.31	1.25±0.35	1.15±0.31	0.427
LDL-C(umol/L)	3.54±1.81	3.70±2.17	3.49±1.47	3.04±1.18	0.282
HbA1c(%)	6.87±1.64	6.83±1.48	6.98±1.87	6.60±1.25	0.584
Concomitant medications n(%)					
ACEI/ARB	208(100.0)	95(100.0)	90(100.0)	23(100.0)	
β-blocker	205(17.8)	93(17.8)	90(17.8)	22(17.8)	0.226
CCB	12(5.8)	6(6.3)	5(5.6)	1(4.3)	0.930

Variables	Total (n=208)	Non-LOF (n=95)	LOF(n=113)		*P*
			Unupgrade Group (n=90)	Upgrade Group (n=23)	
Statins	206(99.0)	94(98.9)	90(100.0)	22(95.7)	0.161
PPI	206(99.0)	94(98.9)	89(98.9)	23(100.0)	0.881
Heart condition					
LVEF(%)	54.77±9.21	54.86±8.75	53.97±10.20	57.57±6.24	0.246
LAD n(%)	109(52.4)	51(53.7)	46(51.1)	12(52.2)	0.940
≥3 branch lesions	75(36.1)	35(36.8)	27(30.0)	13(56.5)	0.060
Stents	1.45±0.86	1.51±0.92	1.31±0.68	1.74±1.14	0.069

UA:unstable angina;STEMI:ST-segment elevation myocardial infarction; NSTEMI:Non-ST-segment elevation myocardial infarction; ACE: angiotensin-converting enzyme; ARB : angiotensin eceptor blocker; PPI:proton pump inhibitor;LVEF: Left ventricular ejection fraction; LOF:loss-of-function;TIA : transient ischemic attack.

4. Results of three groups of clinical follow-up

Table 5 shows a total of 26 cases occurred during the follow-up period MACE, of which Non-LOF allele occurred in 1 case of cardiogenic death. The chi-square test was used to compare the MACE among the three groups during the follow-up period of one year, and it was found that there were significant differences between the three groups (P<0.05), among which the overall MACE rate was (6.3%)vs(18.9%)vs(13.0%). The re-use of Bonferroni method for inter-group comparison suggested that the incidence of unstable angina re-entry and overall MACE in the LOF allele-free group was the highest and significantly different from that in the Non-LOF allele-free group (P<0.05), and no significant difference from the LOF allele-free group (*P*<0.05). There was no significant difference between Non-LOF allele and LOF allele (P>0.05).

Table 5
Results of three groups of clinical follow-up

MACE n(%)	Non-LOF(n=95)	LOF(n=113)		*P*
		Unupgrade Group (n=90)	Upgrade Group (n=23)	
Cardiogenic death	1(1.1)	0(0.0)	0(0.0)	1.000
Relapse into unstable angina	2(2.1)	10(11.1)*	1(4.3)	0.038
Myocardial infarction	1(1.1)	2(2.2)	0(0.0)	0.728
Stent stenosis or thrombosis	1(1.1)	3(3.3)	1(4.3)	0.333
Ischemic stroke	0(0.0)	2(2.2)	0(0.0)	0.395
Bleeding	1(1.1)	0(0.0)	1(4.3)	0.209
Total	6(6.3)	17(18.9)*	3(13.0)	0.035

* P<0.05 compared with Non-LOF allele

Discussion

DAPT composed of aspirin and P2Y12 receptor inhibitors are PCI standard treatments[10]. Different P2Y12 receptor inhibitors (clopidogrel, pragrel, tigrilol) have different levels of potency, enabling physicians to consider individualized and precise treatment options. in reality, switching between inhibitors driven P2Y12 clinical and socio-economic factors has become increasingly common. From clopidogrel to pragrel or tigrelo (known as "upgrade ") or from pratogrel or tigrelo to clopidogrel (known as" downgrade ") has become a major area of research[11]. Actually individualized precision switching DAPT strategies can be selected according to the clinical context (chronic coronary syndrome versus acute coronary syndrome), the stage of the disease (early versus long term), and the risk of ischemic and bleeding complications in patients. Although recent guidelines do not recommend the routine use of gene and platelet function testing in patients with PCI therapy, the application of gene and platelet function testing in individualized precision therapy has been paid more attention[5].

1. CYP2C19 Gene Polymorphism and Population Distribution

CYP2C19 is a highly polymorphic gene. more than 30 allelic variants[12] have been recorded and named by the * allele the human cytochrome P 450(CYP 450) allele nomenclature database. There is increasing evidence that CYP2C19 enzyme belongs to the second subfamily of CYP450 enzymes and is a key enzyme in metabolic process, and its related genes are polymorphic expression[13]. The *1 allele is associated with normal enzyme activity and is considered the default allele, polymorphisms associated with altered enzyme activity do not exist. the CYP2C19*2 and *3 alleles are caused by an abnormal splicing site and a precocious termination codon, respectively, which both cause loss of enzymes and are considered alleles for LOF. The *2 allele is 30-35% in Asians[14],*3 allele occurs 5%-10% in Asians[5], and CYP2C19LOF mutation rate is 60% in Asian population[15]. In this study ,113 patients with LOF group, or 54.3%, were similar to previous studies.

2. CYP2C19 Gene Detection Method and Clinical Application

The current gene detection methods of individualized medicine[4] mainly include: PCR direct sequencing method, PCR pyrophosphate sequencing method, quantitative fluorescence PCR method, PCR gene chip method, PCR electrophoresis analysis method, high resolution melting analysis method, allele polymorphism, in situ hybridization, etc. Among them, real-time fluorescence PCR is the most popular because of its high sensitivity, accurate classification and convenient operation. The current clinical practice generally uses proven effective rapid detection methods such as Spartan RX CYP2C19 system[5], Verigene CYP2C19 system[16] for rapid genotyping. it is a FDA approved microarray-based genotyping method. the system is a fully automated genome extraction, preparation and analysis system with an analysis time of about 2 to 4 hours. There is also a portable system with low entry cost STQ3[17], which contains a one-step method CYP2C19 genotyping detection kit (Coyote Bioscience)[4]. compared with other kits, direct use of whole blood without nucleic acid extraction reduces test time and cost. rapid response test reports can be issued within about 75 minutes but for human diagnosis have not been approved. The population studied in this study were all Chinese people, all of them were tested with uniform kit and equipment to ensure the accuracy of the results.

3. Methods and clinical application of platelet detection

Platelets are involved in every pathological link of the ACS and affect the prognosis, so PFT is an independent risk factor to predict the adverse prognosis and bleeding risk of PCI patients, which has been confirmed by many clinical studies and become a consensus[5]. PFT can be used to assess the biological effects of antiplatelet drugs[18]. the main indicator is platelet aggregation rate, which can be repeatedly detected. The current platelet detection methods include :1. optical transmission turbidimetry ,2. multi-electrode coagulation ,3. VerifyNow ,4. thromboelastogram ,5. VASP ,6. Plateletworks analysis ,7. platelet function analyzer (PFA),8. lamina analyzer (Impact-R),9. p-selectin ,10. GP IIb/IIIa receptor detection, and dozens of others. The above methods of platelet function detection are numerous and different methods have their own advantages and disadvantages, which should be adapted to local conditions according to field conditions, clinical evidence

and standardized detection[19]. On the basis of the current application situation in China, it is suggested that the LTA method should be the main method, auxiliary TEG and other detection methods. A classical LTA method was used to detect platelet aggregation rate in this study, which was operated by experienced technicians to ensure accuracy.

4. Relationship between Platelet Reactivity and CYP2C19 Gene Polymorphism

It is well known that there are individual differences in platelet reactivity[18] associated with genetic, cellular, clinical factors such as age, weight, renal function status, etc. There are 20-30% ACS patients with clinical HPR[3], and about 4%-30% of patients with clopidogrel resistance were found by platelet detection[20, 21]. Where genetic factors have a great influence. in EXCELSIOR trials, Hochholzer et al[22] found that the main independent predictors of insufficient antiplatelet response to clopidogrel were CYP2C19*2 carriers. Mega et al[23] found that plasma active metabolites containing at least one CYP2C19LOF allele carrier decreased by 32.4% compared with noncarriers in 162 healthy subjects after taking clopidogrel, and the maximum platelet aggregation rate for clopidogrel response decreased by 9%. Whereas in a study of 1016 chinese ACS patients undergoing drug-coated stent implantation[24], CYP2C19LOF alleles were associated with HPR, and the risk of adverse cardiovascular events a 1-year follow-up period and were more prominent in high-risk populations (e.g., ACS, complex PCI). Similar to the above results, this study suggests that the slow metabolic genotype has a significant effect on platelet aggregation rate and is an independent risk factor for clopidogrel low reactivity.

5. genotype associated with MACE occurrence and guide PCI benefit from postoperative P2Y12 inhibitor escalation

Mega et al[24] performed a Meta analysis of CYP2C19 genotypes and clinical outcomes in 9685 patients (91.3% PCI postoperative patients and 54.5% ACS patients), with 26.3% carrying at least one LOF allele and 2.2% carrying two LOF alleles. the results found a significant increase in the risk of cardiovascular death, myocardial infarction, or cardiovascular disease complex endpoints in patients carrying LOF alleles compared to Non-LOF allele carriers. The results of this study were similar to those of the above studies, and found that there were significant differences between the three groups ($P<0.05$) between the incidence of recurrent and overall MACE of unstable angina pectoris. the inter-group comparison suggested that the LOF allele unupgraded group had the highest and significant difference compared with the Non-LOF allele ($P<0.05$) in the incidence of recurrent and overall MACE of unstable angina pectoris, indicating that the functional deletion gene was associated with MACE occurrence.

Many studies have shown[2, 17, 25] that the use of genotyping to guide the upgrade from clopidogrel to pragrelot after PCI CYP2C19 nonfunctional allele carriers reduces the risk of atherosclerosis. While in patients with stable coronary heart disease undergoing PCI, although CYP2C19 loss of function was observed to be associated with increased risk of ischemia[25], there is still no evidence that genotype-guided P2Y12 inhibitor can benefit. So far, no randomized genotyping trial has been conducted to guide ACS patient P2Y12 inhibitor escalation. TAILOR-PCI study[6] included 5302 patients with PCI due to ACS or stable coronary heart disease who were randomly assigned to gene-directed and routine treatment groups. The routine treatment group was treated with aspirin combined with clopidogrel, and the gene detection group CYP2C19 the gene detection first, and the patients allele were treated with aspirin combined with clopidogrel. patients with LOF alleles were upgraded to tigrilol with clopidogrel, and the incidence of MACE was finally observed after 1 year. as a result, gene testing guided antiplatelet drug selection failed to reduce the incidence of MACE and there was no significant difference in the risk of bleeding events. This study found no significant difference in the incidence MACE Non-LOF allele versus LOF allele upgrade group ($P>0.05$), and no significant benefit after upgrading treatment was found. but this may be related to the LOF allele upgrade group screened in this study were all platelet hyperresponsiveness populations.

6. Platelet testing guidance PCI benefit from P2Y12 inhibitor upgrade after surgery

although platelet function testing can help identify high-risk patients with clopidogrel HPR, treatment escalation should be strongly considered. nevertheless, ACS postoperative use of PFT to guide clopidogrel escalation in patients still has no evidence of benefit[5]. while there is no evidence that the use of PFT guidance therapy in these patients can benefit, if the patient's risk of bleeding is not high and the risk of embolism is high, the use of PFT may also be considered to decide whether to escalate.

RECLOSE 2-ACS study[26] is the first large-scale prospective study to guide clinical individualized selection of antiplatelet drug therapy based on platelet function test results. ACS patients enrolled in 1789 routine PCI procedures at the Italian Careggi Hospital were treated with clopidogrel loading (600mg), followed by maintenance (75mg/d) combined with aspirin for at least 6 months. The LTA method was used to define the platelet aggregation rate≥70% as high residual platelet reactivity (HRPR) and to intervene to increase the dosage of clopidogrel from 150 mg to 300 mg or to convert to thichloropyridine (500-1000mg/d). the incidence of MACE events was followed up within 2 years. The results showed that the incidence MACE events increased significantly in the HRPR group compared with the non- HRPR group, and the intervention did not significantly improve the incidence of MACE events. Subsequent large-scale prospective clinical trial studies of individualized antiplatelet therapy based on the guidance of platelet function testing[5] also focused on negative results, such as GRAVITAS studies[27], TRIGGER-PCI studies[28], ARCTIC studies[29], etc. This study was based on the combination of gene and platelet detection to screen HPR patients for clopidogrel upgrade therapy. the results showed that there was no significant difference in the incidence of clopidogrel upgrade compared with MACE LOF allele upgrade group ($P>0.05$), similar to the above study. But there are also some studies that suggest that individualized antiplatelet drug therapy based on platelet function testing can improve the prognosis of patients, such as MADONNA studies, IDEAL-PCI studies. The reasons for the difference in the above results may be related to the following points: arterial thrombosis is a complex dynamic process that occurs at the damaged site of the intravascular plaque, while platelet function testing is performed in vitro and can only respond to one of the links, which does not truly reflect the state of the whole thrombus and the true condition of the lesion site. At present, there are many and immature methods for platelet function detection, different test methods draw different conclusions and lack uniform standards. Different thresholds and different disease populations were determined HPR the same platelet function test method.

Conclusions

Although gene and platelet testing is not currently recommended in clinical practice, upgrading strategies may be required when the thrombotic risk is greater than the bleeding risk or when the bleeding risk is greater than the thrombotic risk, a downgrade strategy may be required. At this point, genetic and platelet testing can be an optional tool to guide treatment, and the experience accumulated in this area over the past decade has made individualized treatment more accurate[30]. This study retrospectively analyzed patients with both LOF alleles and HPR using an upgrade strategy to verify whether gene and platelet testing benefit PCI postoperative dual-anti-upgrade in ACS patients. Although previous studies and the results were similar, upgrading treatment did not significantly improve the effect of MACE events. but it provides a useful reference for the study of accurate treatment of antiplatelet drugs.

Limitations

This study is a single-center, small sample size study, limited and not continuously selected patients, there may be selective migration, failed to re-test platelet aggregation rate after upgrading, can not reflect the true situation of platelets and changes in platelet function after replacement treatment strategy.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Data Availability Statement: Some or all data, models, or code generated or used during the study are available from the corresponding author by request. (List items.

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