Impact of IRS-1 rs956115 and CYP2C19 rs4244285 Genotypes on Clinical Outcome of Patients Undergoing PCI

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Abstract

Background insulin receptor substrate-1 (IRS-1) rs956115 is associated with vascular risk in patients with coronary artery disease (CAD) and concomitant diabetes. CYP2C19 rs4244285 modulates clopidogrel responsiveness and predicts outcome of CAD. We designed this study to explore the association between IRS-1 rs956115, CYP2C19 rs4244285, and platelet reactivity as well as 1-year outcome in patients with CAD undergoing percutaneous coronary intervention (PCI).

Methods IRS-1 rs956115, CYP2C19 rs4244285 genotypes and platelet reactivity were assessed in 1611 post-PCI patients. Major adverse cardiovascular events (MACE) which were defined as a composite of cardiovascular death, myocardial infarction and ischemic stroke over 1-year were evaluated. One-way ANOVA was used to compare the platelet reactivity among different genotypes of rs956115 and rs4244285. Multivariable Cox proportional hazard model analysis was used to estimate the association between genotypes of rs956115 and rs4244285 and risk of MACE.

Results At 1 month, patients with rs956115 CG genotype had significantly lower level of residual ADP-induced platelet aggregation (PL_{ADP}) than those with CC genotype. PL_{ADP} significantly increased with the number of rs4244285 A alleles. Patients with rs956115 CG or GG genotype had a 2.09-fold higher risk of MACE than those with CC genotype (adjusted HR=2.09; 95%CI:1.04-4.19; *P*=0.0376), and those with rs4244285 GA genotype had a 2.19-fold higher risk than GG homozygotes (adjusted HR=2.19; 95%CI:1.13-4.24; *P*=0.0200). There was no significant difference in risk between AA and GG homozygotes. No interaction between rs956115 and rs4244285 was observed.

Conclusions In post-PCI patients, rs956115 GG/CG and rs4244285 GA genotypes were associated with 2.09- and 2.19-fold cardiovascular risks respectively at 1-year follow-up. The effect of rs956115 appeared to be independent of known clinical predictors, while that of rs4244285 GA could be mediated by lower clopidogrel response.

Trial registration: Pharmacogenetic and Pharmacokinetic Study of Clopidogrel (PPSC), NCT01968499. Registered October 17, 2013 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT01968499?term=NCT01968499&draw=1&rank=1

Background

Insulin receptor substrate-1 (IRS-1), a ligand of insulin receptor tyrosine kinase, plays a central role in insulin signal transduction system (1, 2). Dysregulation of IRS-1 has been suggested as a common mechanism underlying insulin resistance which may lead to high platelet reactivity and low response to antiplatelet treatment in patients with type 2 diabetes mellitus (DM) (3, 4).

CYP2C19 is one of the isoenzymes of hepatic cytochrome P450 (CYP450) system which plays a key role in the bioactivation of clopidogrel(5, 6). Carriers of CYP2C19 loss of function *2 (rs4244285) generate less amounts of active metabolite of clopidogrel than wild-type homozygotes, which subsequently resulting in a lower clopidogrel responsiveness and an increased risk of major adverse cardiac events in coronary artery disease (CAD) patients after percutaneous coronary intervention (PCI)(7–9).

This study examined the association between IRS-1 rs956115, CYP2C19 rs4244285 and platelet reactivity as well as major adverse cardiovascular events (MACE) in patients with CAD who had undergone PCI and were treated with aspirin and clopidogrel.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This was a prospective single-center cohort study conducted in the First Affiliated Hospital of Nanjing Medical University, Nanjing, China. Complying with the Helsinki declarations and local regulations, the study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University. Written informed consent was obtained from each patient.

The inclusion criteria were patients with CAD undergoing urgent or elective coronary stent implantation who were over 18 years old and planning to take dual antiplatelet treatment (DAPT) with clopidogrel 75 mg and aspirin 100 mg once daily for at least 1 year. Patients who met any of the following criteria were excluded: (1) allergic or intolerant to aspirin or clopidogrel; (2) at high risk of bleeding (e.g., platelet count $<80\times10^9$/L, known bleeding diathesis, active peptic ulcer, or with a history of cerebral hemorrhage within 1 year); and (3) planning to take drugs that could potentially interfere with the antiplatelet effects of aspirin (e.g., non-steroidal anti-inflammatory drugs) or clopidogrel (e.g., CYP3A inhibitors or CYP3A inducers). Baseline demographic and clinical characteristics, as well as medical and interventional treatments, were collected on a pre-specified case report form.

Sample Collection and Preparation

After receiving >5 days of aspirin and clopidogrel, blood was collected 2 hours post dosing (about 10am) from each patient into one 2-mL BD Vacutainer tube (Becton, Dickinson and Company, Franklin Lakes, NJ) containing 3.6 mg K2 EDTA and two 2-mL BD vacutainer tubes with 0.105 mol/L buffered sodium citrate (3.2%). Blood samples were transferred to the central laboratory within 1 hour after collection. Samples in EDTA tubes were frozen at −80°C for genotyping, whereas citrated samples were immediately processed for platelet aggregation studies. After centrifuging the citrated sample at 200g for 8

minutes at 22°C, platelet-rich plasma was carefully separated, and the remaining sample was centrifuged at 2465g for another 10 minutes to obtain platelet-poor plasma. The platelet count in platelet-rich plasma was standardized by addition of platelet-poor plasma to achieve a count of 250×10^9/L. Platelet aggregation tests by light transmission aggregometry were performed within 3 hours of platelet-rich plasma preparation (10). At 1-month follow-up, patients received repeat blood collection for measurement of platelet reactivity as performed at baseline.

Platelet Reactivity Assay

Platelet aggregation testing was performed using a Chronolog Model 700 aggregometer (Chronolog Corporation, Havertown, PA). Immediately after preparation of platelet-rich plasma, 500 μL was transferred into each of the 2 test tubes, with 500 μL platelet-poor plasma as control. Platelet aggregation was induced using adenosine diphosphate (ADP) or arachidonic acid (AA) as agonists with final concentrations of 5 umol/L and 1 mmol/L, respectively. The ADP and AA-induced platelet aggregations (PL_{ADP} and PL_{AA}, respectively) were recorded using the maximum platelet aggregation within 8 minutes.

Genotype Analysis

IRS-1 (rs956115, C>G) and CYP2C19*2 (rs4244285, G>A) were genotyped using a custom-by-design improved multiplex ligation detection reaction technique (Genesky Biotechnologies Inc, Shanghai, China) based on the highly specific double ligation and the multiplex fluorescence polymerase chain reaction (11). For quality control, repeated testing was performed randomly in 5% of samples with high DNA quality.

Clinical Follow-up

Patients were followed-up for 12 months by 2 investigators who were blinded to the results of platelet reactivity testing and genotyping. The patients were followed in the clinic or by telephone if they were unable to attend the clinic. The primary endpoint was defined as the occurrence of MACE, a composite of cardiovascular death, myocardial infarction, and ischemic stroke within 12 months after PCI. The cardiovascular events in this study were defined according to the American College of Cardiology 2001 (12).

Statistical Analysis

Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR) when data did not follow a normal distribution, and differences between groups were analyzed by *t* test or nonparametric test. Categorized variables were expressed as numbers and percentages and were analyzed by χ^2 test or Fisher exact method. One-way ANOVA was used to compare the platelet reactivity among different genotypes of rs956115 and rs4244285. Multivariable Cox proportional hazard model analysis was used to estimate the association between genotypes of rs956115 and rs4244285 and risk of MACE reported as hazard ratio (HR) and 95% confidence intervals (CI). The model was adjusted for clinical covariables including age, previous myocardial infraction (MI), hypertension, diabetes mellitus, smoking status, previous PCI, left ventricular ejection fraction (LVEF), serum creatinine, low density lipoprotein, and diagnosis.

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina) and figures were developed using R, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P value of <0.05 was considered statistically significant.

Results

From Mar 2011 to September 2016, 2213 patients were consecutively screened, among whom 1614 patients who met the inclusion and the exclusion criteria were enrolled. Of the 1614 enrolled patients, 3 were not included in the final analysis due to unsatisfactory blood sample quality. All the remaining patients completed the genotype assessment and 1-year clinical follow-up. Platelet aggregation testing were performed in 1175 patients at baseline and in 624 patients at 1-month follow-up (Figure 1).

Patients' Characteristics

The baseline characteristics of patients included in this study are summarized in Table 1. Compared with patients who did not experience MACE, those who experienced MACE were older [69.00 (14.50) *vs.* 64.00 (15.00), *P*=0.0069], more commonly had reduced LVEF (25.0% *vs.* 7.66%, *P*<0.001) and history of ST-segment-elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndromes (NSTE-ACS) (63.63% *vs.* 42.44%, *P*=0.0010).

Table 1
Baseline Characteristics of Patients Grouped by the Occurrence of MACE

Variables	MACE (n=44)	MACE free (n=1, 567)	*P* value
Age, median (IQR), years	69.00 (14.50)	64.00 (15.00)	0.0069
Sex, No. (%)			0.2966
Female	8(18.18)	393(25.08)	
Male	36(81.82)	1174(74.92)	
Previous MI, No. (%)			0.7166
No	42(95.45)	1499(95.66)	
Yes	2(4.55)	68(4.34)	
Hypertension, No. (%)			0.4109
No	12(27.27)	520(33.18)	
Yes	32(72.73)	1047(66.82)	
Diabetes Mellitus, No. (%)			0.3568
No	30(68.18)	1165(74.35)	
Yes	14(31.82)	402(25.65)	
Smoking, No. (%)			0.3503
No	24(54.55)	743(47.42)	
Yes	20(45.45)	824(52.58)	
Previous PCI, No. (%)			0.4246
No	42(95.45)	1424(90.87)	
Yes	2(4.55)	143(9.13)	
LVEF, No. (%)			<0.001
≥ 55%	33(75.00)	1447(92.34)	
< 55%	11(25.00)	120(7.66)	
Serum creatinine, No. (%)			0.2168
≤ 133μmol/L	42(95.45)	1537(98.09)	
> 133μmol/L	2(4.55)	30(1.91)	
Low density lipoprotein, No. (%)			0.5350
≥ 1.8mmol/L	36(81.82)	1335(85.19)	
< 1.8mmol/L	8(18.18)	232(14.81)	
Diagnosis, No. (%)			0.0010
SA	16(36.36)	902(57.56)	
NSTE-ACS	12(27.27)	412(26.29)	
STEMI	16(36.36)	253(16.15)	

Values are presented as median (IQR) or number of patients (percentage) as appropriate. *P* values were calculated with the use of *t* test or χ^2 test as appropriate. Abbreviations: LVEF. left ventricular ejection fraction; MACE. major adverse cardiovascular events, including cardiovascular death, myocardial infarction and ischemic stroke; MI. myocardial infarction; NSTE-ACS. non-ST-segment elevation acute coronary syndromes; PCI. percutaneous coronary intervention; SA. stable angina pectoris; STEMI. ST-segment-elevation myocardial infarction.

On-Treatment Platelet Reactivity and Genotypes.

The baseline and 1-month PL_{ADP} were (29.88±14.34)% and (26.27±15.10)%, respectively. There was no significant difference in PL_{ADP} among different rs956115 genotypes at the baseline assessment (*F*=0.20, *P*=0.8200, Figure 2A). At 1-month follow-up, PL_{ADP} was significantly different among the three genotypes (*F*=3.28, *P*=0.0381, Figure 2A). CG genotype was associated with a significantly lower PL_{ADP} compared with CC genotype (*P*=0.0158, Figure 2A). Regarding PL_{AA}, there were no significant difference among the three genotypes of rs956115 either at baseline (*F*=2.73, *P*=0.0656, **Figure S1A**) or at 1-month follow-up (*F*=0.20, *P*=0.8180, **Figure S1A**).

For rs4244285, PL_{ADP} were significantly different among the three genotypes at baseline (F=53.27, P<0.001, Figure 2B) and 1-month follow-up (F=12.07, P<0.001, Figure 2B). By pairwise comparisons, the platelet reactivities corresponding to different genotypes of rs4244285 were all significantly different except the comparison between GA and AA at 1-month follow-up (P=0.4392, Figure 2B). As shown in Figure 2B, the platelet reactivity increased with the number of the A alleles of rs4244285. Regarding PL_{AA}, there were no significant difference among the three genotypes of rs4244285 either at baseline (F=0.38, P=0.6870, **Figure S1B**) or at 1-month follow-up (F=0.78, P=0.4590, **Figure S1B**).

Association between IRS/CYP2C19 Genotypes and Cardiovascular Outcomes.

A total of 44 patients experienced MACE, including 15 cardiac deaths, 16 nonfatal myocardial infarctions, and 13 ischemic strokes.

For rs956115, patients with CG or GG genotypes had a 1.99-fold higher MACE risk than those with CC homozygote (dominant model, adjusted HR=1.99, 95%CI: 1.00-3.98, P=0.0499; additive model, adjusted HR=1.95, 95%CI: 1.05-3.61, P=0.0341; Table 2). When further adjusted for rs4244285 genotypes, patients with CG or GG genotypes had a 2.09-fold higher MACE risk than those with CC homozygote (dominant model, adjusted HR=2.09, 95%CI: 1.04-4.19, P=0.0376; additive model, adjusted HR=2.04, 95%CI: 1.10-4.19, P=0.0244; Table 2 **and** Figure 3A). There was no significant difference in risk of MACE risk between CG and CC genotypes (adjusted HR=1.91, 95%CI: 0.94-3.88, P=0.0751) or between GG and CC genotypes (adjusted HR=4.23, 95%CI: 0.55-32.29, P= 0.1643) (Table 2).

Table 2
MACE risk by Multi-Cox regression

SNP	Gene	Geno-type	MACE N	Censored N	Comparison	Unadjusted model		Adjusted model [a]		Adjusted model [b]	
						HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P va
rs956115	IRS1	CC	32	1245		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
		CG	11	305	CG *vs.*CC	1.66(0.82,3.34)	0.1571	1.91(0.94,3.88)	0.0751	1.99(0.98,4.08)	0.
		GG	1	17	GG *vs.*CC	2.65(0.36,19.53)	0.3377	4.23(0.55,32.29)	0.1643	4.70(0.62,35.84)	0.
					Dominant	1.71(0.87,3.38)	0.1211	1.99(1.00,3.98)	0.0499	2.09(1.04,4.19)	0.
					Recessive	2.35(0.32,17.11)	0.3992	3.58(0.48,26.96)	0.2157	3.91(0.52,29.33)	0.
					Additive	1.65(0.91,3.00)	0.1013	1.95(1.05,3.61)	0.0341	2.04(1.10,3.81)	0.
rs4244285	CYP2C19	GG	14	712		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
		GA	28	666	GA *vs.*GG	2.04(1.07,3.90)	0.0303	2.13(1.10,4.12)	0.0248	2.19(1.13,4.24)	0.
		AA	2	189	AA *vs.*GG	0.60(0.14,2.65)	0.5010	0.58(0.13,2.61)	0.4814	0.58(0.13,2.60)	0.
					Dominant	1.76(0.93,3.33)	0.0843	1.81(0.94,3.49)	0.0759	1.85(0.96,3.56)	0.
					Recessive	0.40(0.10,1.65)	0.2049	0.37(0.09,1.56)	0.1767	0.37(0.09,1.53)	0.
					Additive	1.17(0.75,1.82)	0.4853	1.16(0.74,1.81)	0.5114	1.17(0.75,1.81)	0.

[a] Model adjusted for clinical covariates, including age, previous MI, hypertension, diabetes mellitus, LVEF, serum creatinine, diagnosis, low density lipoprotein, smoking status, previous PCI. [b] Model adjusted for rs4244285/ rs956115 and clinical covariates, including age, previous MI, hypertension, diabetes mellitus, serum creatinine, diagnosis, low density lipoprotein, smoking status, previous PCI. Dominant model: CG and GG *vs.*CC. Recessive model: GG *vs.*CC and CG. Addictive model: the number of risk alleles is proportional to the risk of MACE. Abbreviations: CI, confidence intervals; HR, hazard ratio; Other abbreviations as Table 1.

For rs4244285, patients with GA genotype had a 2.13-fold higher MACE risk than those with GG genotype (adjusted HR=2.13, 95%CI: 1.10-4.12, P=0.0248; Table 2). Patients with AA genotype showed no increased MACE risk to GG genotype (adjusted HR=0.58; 95%CI:0.13-2.60; P=0.4787). When further adjusted for rs956115 genotypes, patients with GA genotype had a 2.19-fold higher risk than those with GG genotype (adjusted HR=2.19, 95%CI: 1.13-4.24, P=0.0200; Table 2 **and** Figure 3B). No significant difference of MACE risk was found while using either dominant (P=0.0666; Table 2) or additive model (P=0.4936; Table 2).

Interaction Analysis

Among patients with GG genotype of rs4244285, those who had CG or GG genotype of rs956115 presented a 4.85-fold higher MACE risk than those who had CC genotype (adjusted HR=4.85, P=0.0081; Figure 4). By comparison, among patients with non-GG genotype of rs4244285, those who had CG or GG genotype of rs956115 presented a 1.40-fold higher risk than those who had CC genotype (adjusted HR=1.40, P=0.4764; Figure 4). The interaction between rs956115 and rs4244285 was none-statistically significant (P=0.1453; Figure 4).

Association Of Rs956115 With Mace In Subgroup Analysis

We performed multivariable Cox-regression analysis for rs956115 in different patient subgroups (Figure 5). The association between rs956115 genotypes and MACE remained statistically significant in subgroup of normal serum creatinine (adjusted HR=2.09, 95%CI: 1.04-4.18) (Figure 5). Although the adjusted HR

between CG or GG and CC genotypes of rs956115 did not reach statistically significant in the diabetes subgroup (Figure 5), the dominant model HR of MACE for patients with CG or GG genotype of rs956115 tended to be similar across subgroups. No significant interactions were observed in any of those subgroups except LVEF subgroup (Interaction *P*=0.0006) (Figure 5).

Discussion

This study examined the impacts of IRS-1 rs956115 and CYP2C19 rs4244285 polymorphisms on clinical outcome of patients undergoing PCI and receiving DAPT treatment and found that G allele carriers of IRS-1 rs956115 had a 2.09-fold higher risk of MACE compared with non-carriers at 1-year follow-up. The rs4244285 GA genotype had a 2.19-fold higher risk than GG homozygotes. The effect of rs956115 was independent to known clinical covariables, while that of rs4244285 GA could be mediated by lower clopidogrel response.

Angiolillo et al. examined 7 single nucleotide polymorphisms (SNPs) of IRS-1 and found that rs956115 polymorphism was associated with a hyperreactive platelet phenotype and adverse cardiovascular outcomes in type-2 DM Caucasian patients concomitant with coronary artery disease (CAD) (13). However, uncertainty remains about the effects of IRS-1 rs956115 polymorphism on platelet function and cardiovascular outcome in non-selective CAD patients.

In this study, we found that rs956115 G allele was an independent prognostic factor of adverse cardiovascular outcomes in non-selective CAD patients, irrespective of CYP2C19*2 (rs4244285) polymorphism, diabetes mellitus and other known risk factors. Although rs956115 G allele didn't show a significant correlation with MACE in the subgroup of diabetes mellitus, our results showed the consistent tendency of almost all subgroups as shown in Figure 5.

Regarding the underlying mechanism, *Angiolillo et al* suggested that rs956115 polymorphism was associated with a hyperactive platelet phenotype in Caucasian type-2 DM patients (13). However, in a later study by *Zhang et al*, no association was observed between rs956115 polymorphism and platelet function profile (14). Our results were in consistent with that of *Zhang et al* in a larger Chinese population, showing no significant difference in AA or ADP-induced platelet aggregation at baseline among different IRS-1 rs956115 genotypes. Moreover, ADP-induced platelet aggregation was even lower in rs956115 CG genotype compared with CC genotype at 1-month follow-up. Along with the results of *Zhang's* study, we suggest that the association between IRS-1 rs956115 polymorphisms and risk of MACE cannot be explained by impaired platelet reactivity to either clopidogrel or aspirin.

Theoretically, IRS-1 is one of the central nodes in insulin signaling network (15). It has been reported that IRS-1 is necessary for insulin-stimulated activation of phosphatidylinositol 3 kinase (PI3K)/AKT pathway and subsequent enhanced production of nitric oxide (NO) in endothelial cells (16), which plays a critical role in maintaining cardiovascular homeostasis (17). Previous studies have demonstrated that functional variants of IRS-1 directly impaired insulin regulated NO synthesis in cultured human endothelial cells (18, 19). Considering the pivotal role of IRS-1 in PI3K/AKT signaling pathway of insulin, it may be reasonable to assume IRS-1 rs956115 polymorphism affects the same process or an unknown pathway and consequently impacts the clinical outcome of CAD patients.

Our results were consistent with previously reports and further confirmed that CYP2C19*2 (rs4244285) loss of function polymorphism is a strong predictor of impaired clopidogrel response and adverse clinical outcomes (7–9). This consistency, in turn, enhances the credibility of our results on rs956115. Meanwhile, from the interaction analysis, we did not find a statistically significant interaction between IRS-1 rs956115 and CYP2C19 rs4244285 polymorphism, which proved IRS-1 rs956115 G allele to be an independent risk factor of MACE in CAD patients after PCI.

Conclusions

IRS-1 rs956115 G allele significantly increased the cardiovascular risk of post-PCI patients by 2.09-fold at 1-year follow-up, which was independent to CYP2C19 rs4244285 genotypes, pharmacological platelet response and known clinical covariables.

Declarations

Ethics approval and consent to participate

Complying with the Helsinki declarations and local regulations, the study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University. Written informed consent was obtained from each patient.

Consent for publication

As stated above, informed consent on participation and publication was obtained from all participants.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CL contributed to the conceptualization and supervision of the study, review and editing the manuscript. YZ contributed to the supervision of the study, interpretation of the data, review and editing the manuscript. JZ contributed to the investigation of the patients, writing the original draft. YT contributed to interpretation of the data, writing the original draft. IU, TW, KX, PC, ZC, JW, TZ, JC, JL, FW, LY, YF, LS, XG contributed to the investigation of the patients. All authors read and approved the final manuscript.

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Figures

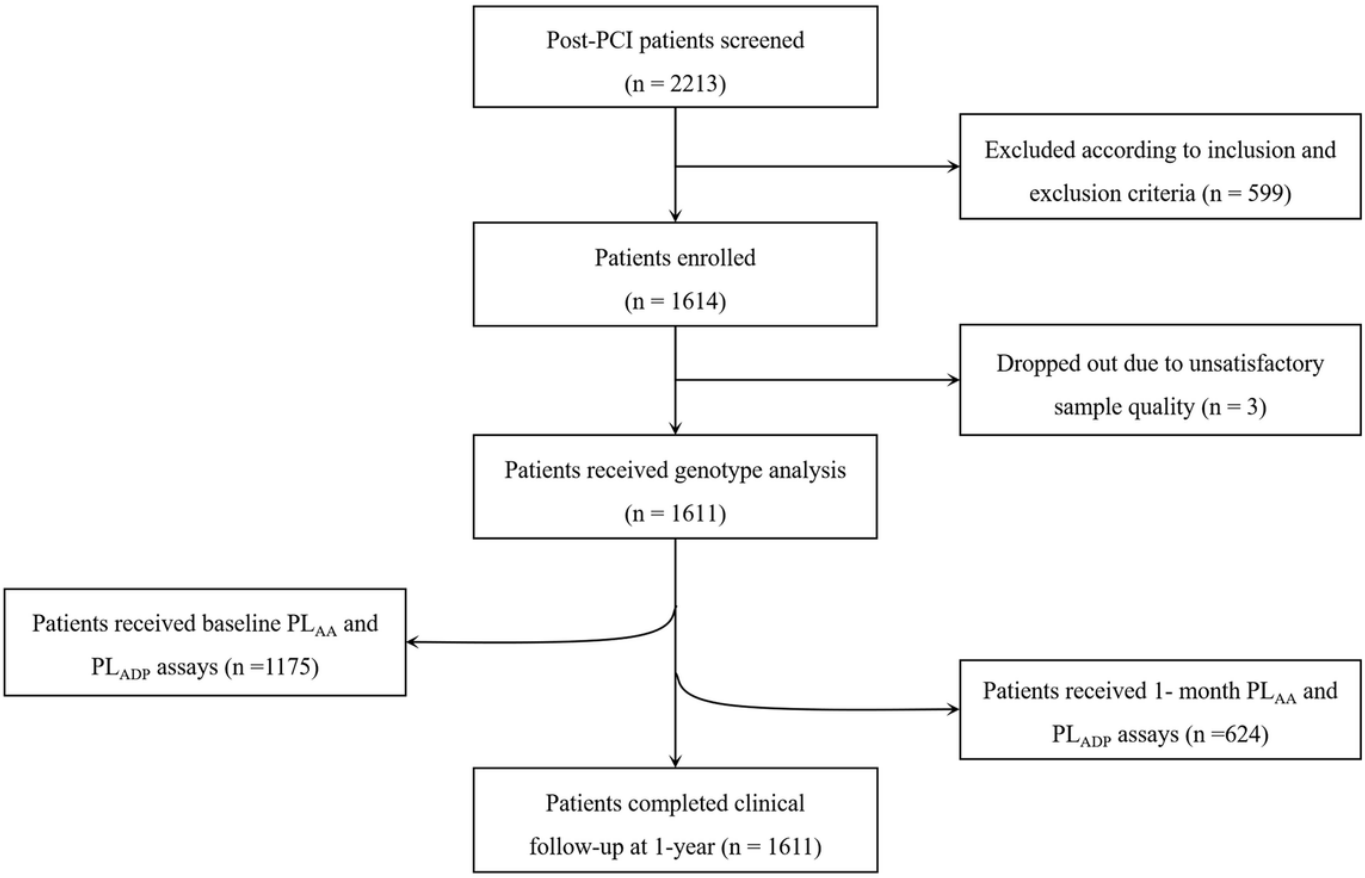

Figure 1

Study flow chart. Abbreviations: PLADP, adenosine diphosphate induced platelet aggregation.

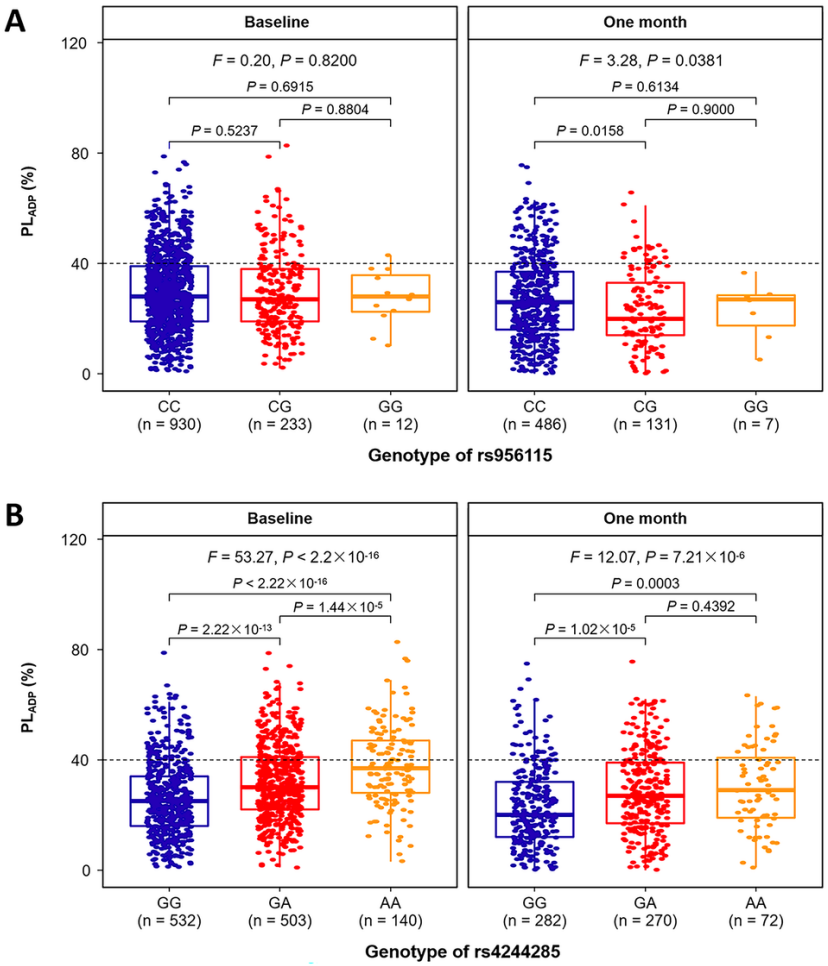

Figure 2

Platelet reactivities (PLADP) in patients with different genotypes of rs956115 and rs4244285 (A) Boxplot of rs956115 and PLADP at baseline and 1 month; (B) Boxplot of rs4244285 and PLADP at baseline and 1 month. Abbreviations: PLADP, adenosine diphosphate induced platelet aggregation.

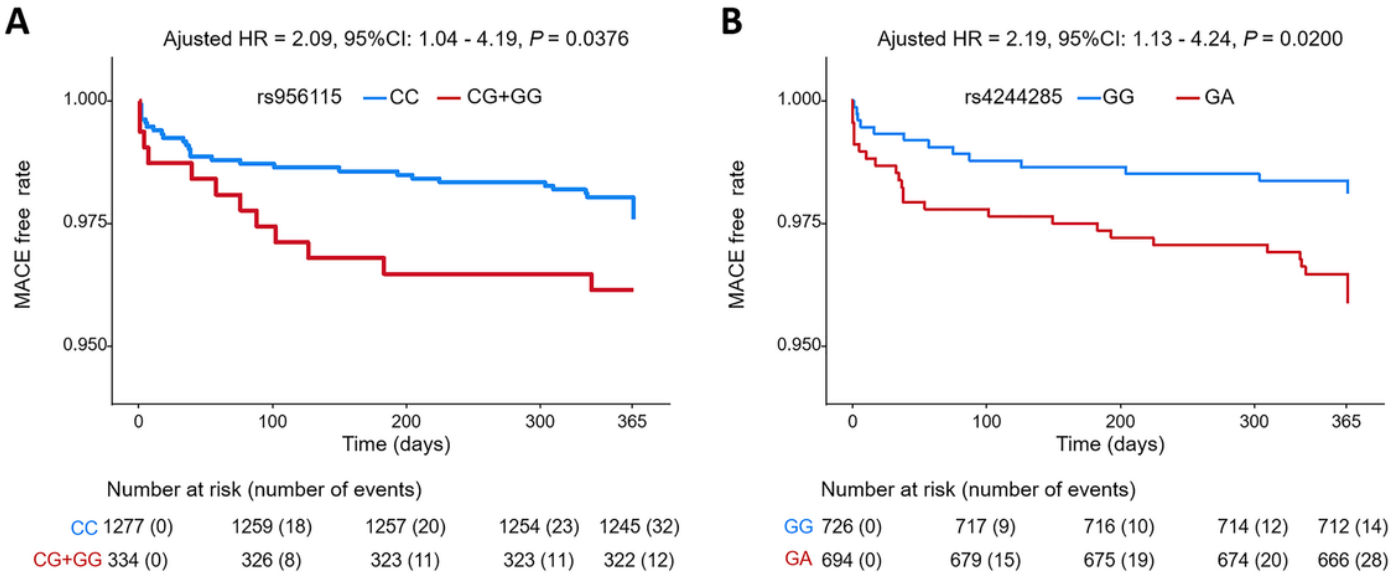

Figure 3

Survival curve of MACE free rate and rs956115/rs4244285. (A) Survival curve of MACE free rate and rs956115. Cox regression model adjusted for rs4244285 and clinical covariates, including age, previous MI, hypertension, diabetes mellitus, smoking status, previous PCI, LVEF, serum creatinine, low density lipoprotein and diagnosis; (B) Survival curve of MACE free rate and rs4244285. Cox regression model adjusted for rs956115 and clinical covariates, including age, previous MI, hypertension, diabetes mellitus, smoking status, previous PCI, LVEF, serum creatinine, low density lipoprotein and diagnosis. Abbreviations: CI, confidence intervals; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

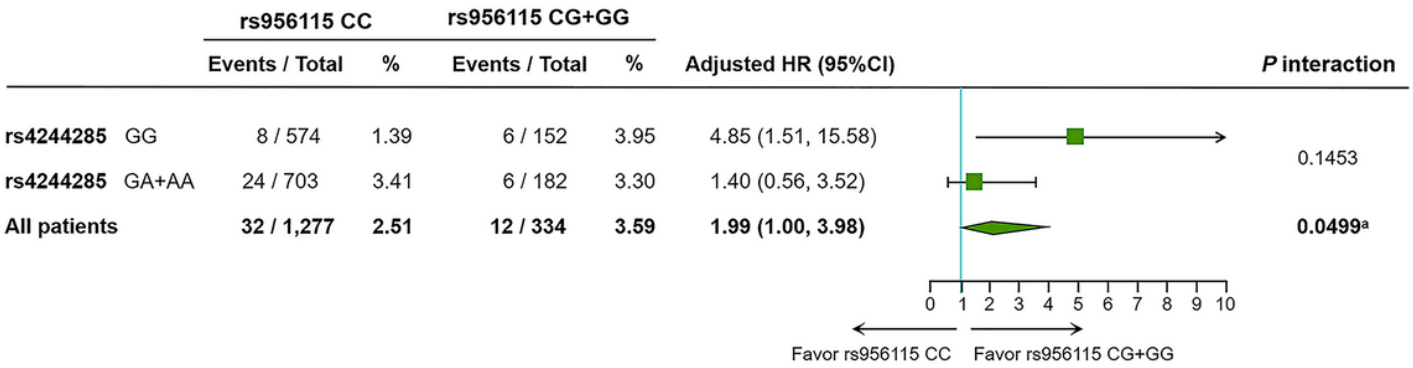

Figure 4

The hazard ratio of rs956115 mutation by different genotypes of rs4244285. Model adjusted for clinical covariates, including age, previous MI, hypertension, diabetes mellitus, smoking status, previous PCI, LVEF, serum creatinine, low density lipoprotein, diagnosis. a P value indicated the association between rs956115 and MACE in all patients.

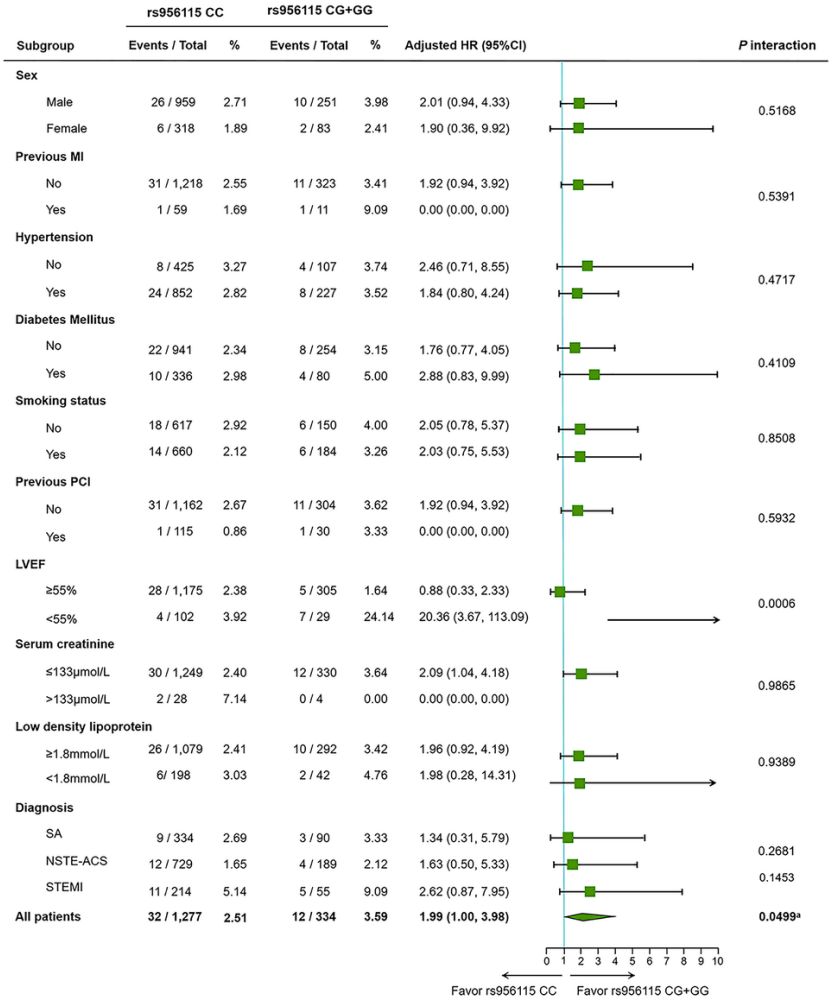

Figure 5

Forest plot of MACE risk in different rs956115 genotypes a P value indicated the association between rs956115 and MACE.

Supplementary Files

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- FigureS1.tif