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ORIGINAL RESEARCH

Association Between ABCB1 Gene Polymorphism with Hyperglycemia and MACE in Patients Undergoing Clopidogrel Treatment After PCI

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Purpose: To evaluate the effect of *ABCB1* C3435T gene polymorphism with hyperglycemia on the risk of major adverse cardiovascular events (MACE) in patients treated with clopidogrel after percutaneous coronary intervention (PCI).

Patients and Methods: A total of 117 patients were studied, of which 52 developed MACE. We used fluorescence in situ hybridization to detect the genotype of the *CYP2C19* and *ABCB1* C3435T loci. Baseline characteristics, fasting blood glucose, and clinical outcomes were collected. Logistic regression was used to analyze factors influencing MACE in PCI patients treated with clopidogrel.

Results: There were significant differences between normal and MACE groups in gender, age, history of diabetes mellitus, history of alcohol consumption, fasting blood glucose, *ABCB1* (CC) with normoglycemia, and *ABCB1* (CT/TT) combined with hyperglycemia ($P < 0.05$). *ABCB1* C3435T genotype ($P= 0.024$, OR = 5.584, 95% CI 1.258–24.780), age ($P= 0.014$, OR = 1.073, 95% CI 1.014–1.135), History of hypertension ($P= 0.020$, OR = 3.144, 95% CI 1.200–8.238) and History of diabetes mellitus ($P= 0.030$, OR = 3.731, 95% CI 1.135–12.270) were independent MACE risk factors. In patients <75 years, history of hypertension ($P= 0.021$, OR = 3.151, 95% CI 1.189–8.350) was a risk factor, while the *ABCB1* (CC) with normoglycaemia ($P= 0.023$, OR = 0.147, 95% CI 0.028–0.767) was a protective factor.

Conclusion: The *ABCB1* C3435T genotype is an independent risk factor for MACE after PCI with clopidogrel therapy. *ABCB1* CC combined normoglycemia may protect against MACE in patients <75 years.

Trial Registration: Registration number: ChiCTR2400082012, Reg Date: 2024-03-19.

Keywords: *ABCB1* C3435T, coronary artery disease, PCI, genetic polymorphism, major adverse cardiac events

Introduction

Coronary atherosclerotic heart disease (CHD) is caused by the narrowing or blockage of coronary arteries due to atherosclerosis, resulting in myocardial hypoxia, ischemia, or necrosis.[1] In recent years, the incidence of CHD has been steadily increasing and has become the leading cause of death worldwide.[2,3] In 2020, the mortality rate of CHD among Chinese urban residents was 126.91 per 100,000, while in rural areas, it was 135.88 per 100,000. Notably, CHD mortality has been increasing from 2012 to 2020, especially in rural areas. Presently, there are approximately 11.39 million CHD patients in China.[4] Percutaneous coronary intervention (PCI) is a crucial treatment option for CHD, reducing the risk of major adverse cardiovascular events (MACE).[5] MACE is defined as a composite endpoint consisting of cardiac death, myocardial infarction, stroke, emergency target vessel reconstruction, stent thrombosis, non-emergency revascularization, unstable angina, atrial fibrillation, and ventricular fibrillation.[6,7] However, there is a possibility of MACE occurrence in the months following PCI,[8]

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with a mortality rate exceeding 5%.[9] Double antiplatelet therapy (DAPT) is the cornerstone of prevention and treatment of cardiovascular disease,[10] and its implementation after PCI effectively reduces the incidence of MACE.[11]

Clopidogrel is one of the DAPT drugs and has been found to exhibit resistance (CR) in approximately 4–30% of patients.[12] The causes and mechanisms of CR occurrence remain unclear. Previous studies have suggested that it is related to age, smoking, diabetes mellitus, hypertension, patient compliance, drug interactions, and genetic polymorphisms.[13,14] As a prodrug, clopidogrel requires absorption and metabolism for its antiplatelet effect. The absorption of clopidogrel in the intestine is influenced by the P-glycoprotein encoded by the *ABCB1* gene,[15] and *CYP2C19* and *PON1* enzymatic metabolism are necessary for the conversion of clopidogrel into its active metabolites in the liver.[16] *CYP2C19* is the key enzyme in the antiplatelet activity of clopidogrel, and *CYP2C19* loss-of-function alleles were associated with MACE.[17–19] *ABCB1* is a member of the ABC family and was first discovered in 1976.[20] Human *ABCB1* was first discovered because of its high expression in cancer cells,[21] as it encodes a P-glycoprotein with exocytosis, which can transport drugs and other substances from the intracellular to extracellular space.[22] Over 50 mutants have been identified, of which C3435T, G2677T/A, and C1236T were the major alleles, the *ABCB1 C3435T* being the most extensive investigation.[23] *ABCB1 C3435T* is located in exon 26 and is highly susceptible to gene synonymous mutations, which can cause changes in the structure of P-gp and subsequently alter its function.[24] Research has shown that the expression level of P-gp mRNA in duodenal epithelial cells of individuals carrying the *ABCB1 C3435T* TT genotype is significantly increased compared to CC and CT.[25] The *ABCB1 C3435T* T allele can enhance efflux and reduce the absorption of clopidogrel, thereby reducing drug efficacy. Importantly, the distribution of *ABCB1* gene polymorphisms varies among races and geographic regions.

Studies have shown that individuals with the *ABCB1 C3435T* TT homozygotes had an increased risk for adverse cardiovascular outcomes during clopidogrel treatment after acute coronary syndrome and PCI.[26] In patients with clopidogrel administration after PCI, the ABCB1 C3435T genetic variant might influence on bleedings.[27] Patients with the *ABCB1 C3435T* TT genotype who underwent PCI had a significantly increased risk of MACE.[23] The *ABCB1 C3435T* CT genotype did not have any effect on the antiplatelet effect of clopidogrel or MACE.[28] Currently, studies on ABCB1 gene polymorphism and MACE risk are controversial. Blood glucose levels in diabetic patients exhibit a positive correlation with P-gp activity.[29] Alterations in P-GP expression and function under diabetic conditions are tissue specific and diabetic duration dependent.[30] Antidiabetic drugs exert regulatory effects on glycemia by inhibiting P-gp activity, thereby promoting intestinal absorption of therapeutic agents.[31] However, existing evidence regarding the impact of diabetes on ABCB1 function remains inconsistent.[32] This study aimed to explore the effect of *ABCB1 C3435T* polymorphism combined with hyperglycemia on the risk of MACE after clopidogrel therapy in PCI patients.

Materials and Methods

Study Participants

In this study, we collected study subjects who were CHD patients hospitalized in Taian Central Hospital for PCI treatment and underwent *CYP2C19* and *ABCB1* C3435T gene testing from 01/06/2018 to 30/09/2021. All patients were followed up at 1, 6, and 12 months after PCI, including outpatient visits and readmission follow-ups. The data were accessed for research purposes from 01/06/2018 to 30/09/2022. Inclusion criteria: 1) Age > 18 years; 2) Meet the diagnostic criteria for coronary artery disease in the Diagnostic and Therapeutic Guidelines for Stable CHD; 3) *CYP2C19* normal metabolic; 4) First PCI treatment; 5) Receiving oral clopidogrel (75 mg orally once a day) combined with aspirin (100 mg orally once a day) for antiplatelet treatment for 12 months, and including patients with MACE during this period; 6) Having complete case data and being followed up until the end event. Exclusion criteria: 1) malignant tumors; 2) Contraindications to antiplatelet therapy; 3) Bleeding disorders; 4) Severe organ insufficiency; 5) Pregnancy or lactation. This study was conducted by the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Affiliated Taian City Central Hospital of Qingdao University (2020 Lunshen No. 60), and informed consent was signed by the patients themselves for cognitive assessment scales >25 and by their families for ≤25.

Reagents and Instruments

Universal sequencing reaction kit, Nucleic acid purification reagents, NH4Cl, Sterilized Water for Injection (500 mL), TL998A Fluorescence detector, Eppendorf high-speed centrifuge 5418, Eppendorf pipettes (10 μL,200 μL,1000 μL), Centrifuge (1.5mL), Pipette tips (10 μL,200 μL,1000 μL), EDTA anticoagulation tubes centrifuge tubes (2 mL).

Experimental Methods

Specimen Collection

A volume of 1.5 mL of venous blood was collected from the patients using EDTA anticoagulation tubes. Mixed thoroughly to prevent hemolysis or coagulation and stored at 4°C low temperatures for no longer 24 h. The blood was stored at −20°C for long-term preservation.

ABCB1 Genetic Polymorphism Detection

1) 1mL of ammonium chloride was added to the centrifuge tube, then add 150 μL of blood and let stand for 5 min; 2) The tube was then centrifuged at 3000 rpm for 5 min, and the supernatant was discarded; 3) 50 μL of nucleic acid purification reagent was added and mixed; 4) 1.5μL of suspension was added to the corresponding universal kit for sequencing reaction. The pipette tip was checked for any liquid residue on its front, and the cap was tightly fastened. The tube was inverted several times to ensure thorough mixing, and the wall of the tube was flicked to remove bubbles from the liquid surface. A microcentrifuge was used briefly to remove droplets attached to the tube's wall, and the resulting mixture was tested against the software number using a machine; 5) Using the TL998A fluorescence detector for testing; 6) The fluorescence profile images were reviewed for genotyping.

Clinical Data Collection

Collected the baseline data of enrolled patients, including age, gender, history of smoking, history of alcohol consumption, history of hypertension, history of diabetes mellitus, *ABCB1* genotype, fasting blood glucose, and homocysteine values at the time of relapse or at the 12th month. All patients received follow-ups at 1, 6, and 12 months after discharge. This follow-ups included outpatient visits and readmission follow-ups. The primary endpoint event during follow-ups was major MACE.

Statistical Analysis

We applied the Hardy-Weinberg law of genetic equilibrium to test the population representativeness of the samples; SPSS 25.0 was used for statistical analysis. Data that followed a normal distribution were presented as Mean ± SD ($\bar{x} \pm s$), and between-group comparisons were conducted using independent samples t-tests. For data that did not follow a normal distribution, the median and interquartile range M (P25, P75), and between-group comparisons were made using the two-sample rank sum test. Count data were expressed as cases (%) and compared between groups using the chi-square (χ^2) test. Logistic regression analysis was used to analyze the factors influencing the occurrence of MACE in patients undergoing PCI. $P < 0.05$ indicates that the difference is statistically significant.

Results

HWE Equilibrium Test

The Hardy-Weinberg genetic balance test for polymorphisms in the *ABCB1* C3435T gene was performed on 117 patients with CHD, and the result of $P > 0.05$ was in accordance with Hardy-Weinberg's law of genetic balance, which indicated that the selected samples were representative of the population, shown in Table 1.

Patients Baseline Characteristics

Among the 117 patients, 52 patients occurred MACE, accounting for 44.4% of the total patients. There were no statistically significant differences between the normal and MACE groups in terms of history of hypertension, history of smoking, homocysteine concentration, *ABCB1* (CC) combined hyperglycaemia, ABCB1 (CT/TT) combined normoglycaemia ($P > 0.05$). However, there were statistically significant differences in terms of gender, age, history of diabetes

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Table 1 The Hardy-Weinberg Equilibrium of ABCB1 C3435T

ABCB1 C3435T	Frequency		χ^2	*P* value
	Measured N (%)	Theoretical N (%)		
CC	29(24.8%)	23(19.7%)	2.169	0.338
CT	47(40.2%)	58(49.6%)		
TT	41(35.0%)	36(30.8%)		

Notes: CC-wild type homozygous, CT-heterozygous and TT-Mutant type homozygous.

Table 2 Baseline Characteristics

Characteristics	Normal Group (65)	MACE Group (52)	*P* value
Male (n, %)	49 (75.4)	29 (55.8)	0.025
Age (years) Mean ± SD	58.82±8.761	64.44±8.974	0.001
History of hypertension (n, %)	32 (49.2)	34 (65.4)	0.08
History of diabetes mellitus (n, %)	11 (16.9)	27 (51.9)	< 0.001
History of smoking (n, %)	25 (38.5)	17 (32.7)	0.518
History of alcohol consumption (n, %)	21 (32.3)	8 (15.4)	0.035
Fasting blood-glucose M (P25, P75)	5.79 (5.33,6.09)	6.52 (5.40,8.09)	0.038
Homocysteine M (P25, P75)	13.4 (11.2,15.8)	13.3 (10.6,17.6)	0.683
TT+ Hyperglycemia (n, %)	4 (6.2)	6 (11.5)	0.482
TT+ Normoglycaemia (n, %)	15 (23.1)	4 (7.7)	0.025
CT/CC+ Hyperglycemia (n, %)	11 (16.9)	22 (42.3)	0.002
CT/CC+ Normoglycaemia (n, %)	35 (53.8)	20 (38.5)	0.098

mellitus, history of alcohol consumption, fasting blood glucose, *ABCB1* (CC) combined normoglycaemia, and *ABCB1* (CT/TT) combined hyperglycaemia were statistically significant ($P < 0.05$), shown in Table 2.

Distribution of ABCB1 C3435T Genotypes in Two Groups

Used fluorescence in situ hybridisation to detect the *ABCB1* C3435T genotype, shown in Figure 1. The T allele mutation rate in the two groups was 53.1% and 57.7%, respectively. The difference of *ABCB1* C3435T genotype and allele frequency was not statistically significant in the two groups ($P > 0.05$), shown in Figure 2.

Multifactorial Logistic Regression Analysis of Factors Influencing MACE After Clopidogrel Treatment in PCI Patients

A multifactorial logistic regression analysis was conducted to examine the relationship between the occurrence of MACE and a variety of factors. The dependent variable was the occurrence of MACE, while the independent variables included gender, age, *ABCB1* C3435T genotype, history of hypertension, history of diabetes mellitus, history of smoking, history of alcohol consumption, fasting blood glucose, homocysteine concentration, and *ABCB1* C3435T genotype with blood glucose value. The results of the analysis showed that *ABCB1* C3435T genotype (*P*= 0.024, OR = 5.584, 95% CI 1.258–24.780), age (*P*= 0.014, OR = 1.073, 95% CI 1.014–1.135), History of hypertension (*P*= 0.020, OR = 3.144, 95% CI 1.200–8.238) and History of diabetes mellitus (*P*= 0.030, OR = 3.731, 95% CI 1.135–12.270) were independent MACE risk factors, shown in Table 3.

Logistic Regression Analysis of Risk Factors for MACE After Clopidogrel Treatment in PCI Patients Aged < 75 years

Excluded Patients aged >75 years. A total of 108 study subjects underwent one-way logistic regression analysis, where independent variables with a significance level of $P < 0.1$ were included in the regression equations. This was followed by multifactorial logistic regression analysis. The results of the analysis showed that history of hypertension (*P*= 0.021,

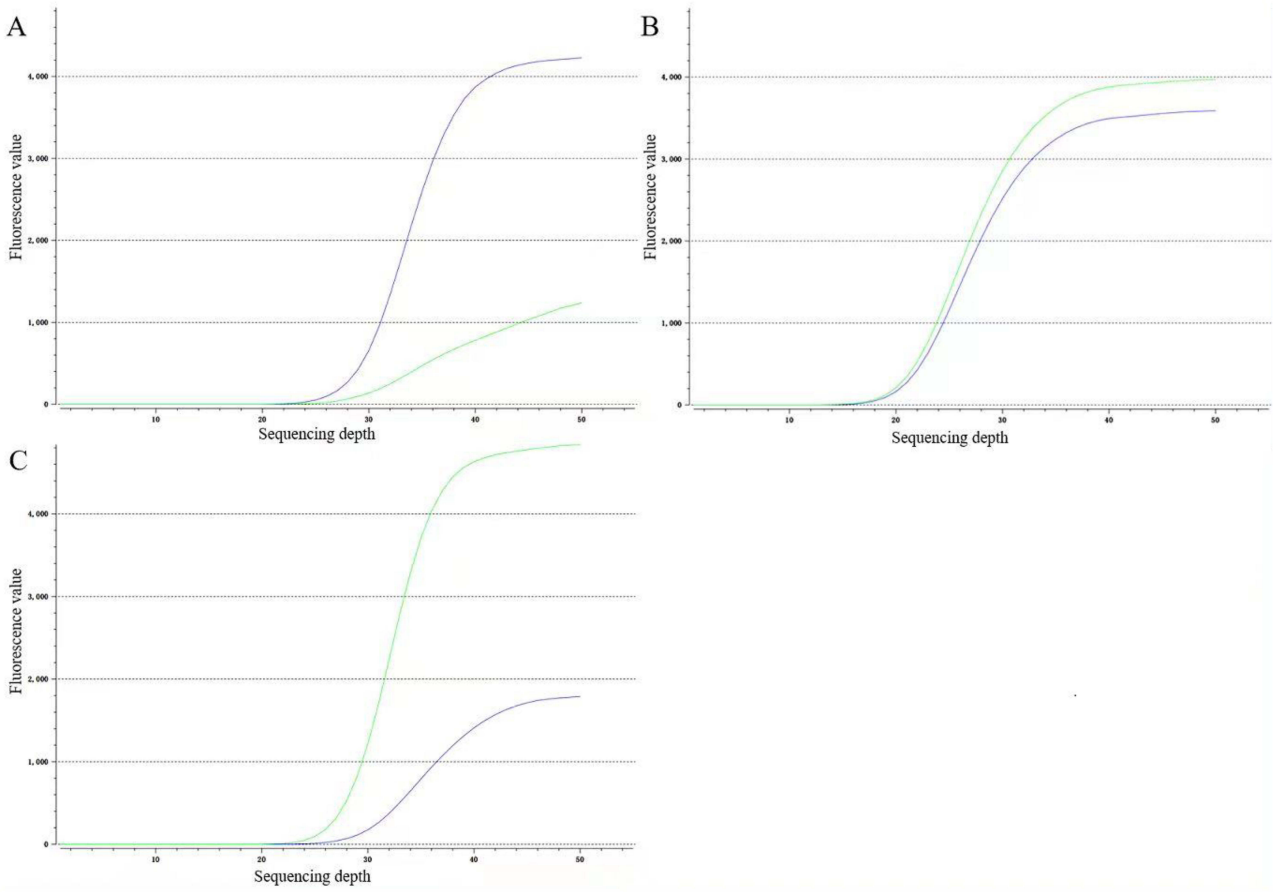

Figure 1 The sequencing line of *ABCB1 C3435T* genotypes. (**A**) CC, (**B**) CT and (**C**) TT.

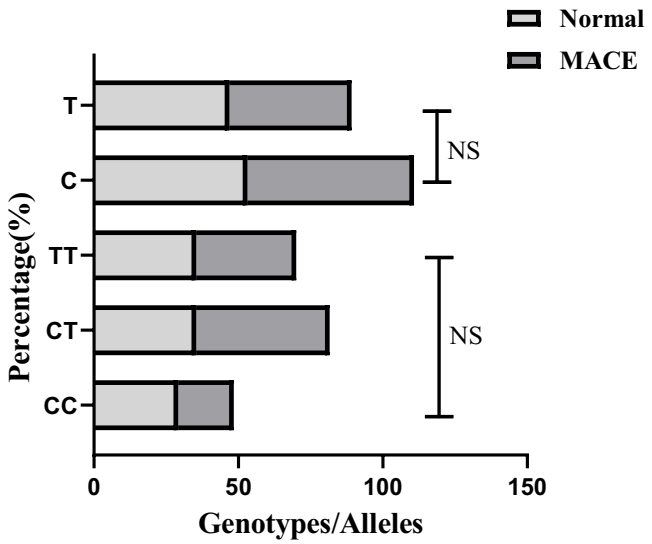

Figure 2 Distribution of *ABCB1 C3435T* genotype in Normal and MACE group.

OR = 3.151, 95% CI 1.189–8.350) was an independent risk factor for MACE after clopidogrel treatment in PCI patients. Additionally, the *ABCB1* (CC) with normoglycaemia (P= 0.023, OR = 0.147, 95% CI 0.028–0.767) was a protective factor for MACE after clopidogrel treatment in PCI patients, detailed in Table 4.

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Table 3 Multivariate Logistic Regression Analysis of MACE in PCI Patients

	ItermS	B	SE	Wald	*P* value	Exp (B)	EXP (B) 95.0% CI
Gender	0*						
	1	1.006	0.644	2.440	0.118	2.734	0.774–9.656
Age		0.071	0.029	6.011	0.014	1.073	1.014–1.135
ABCB1 (C3435T)	0*						
	1	1.720	0.760	5.117	0.024	5.584	1.258–24.780
History of hypertension	0*						
	1	1.146	0.491	5.434	0.020	3.144	1.200–8.238
History of diabetes mellitus	0*						
	1	1.317	0.607	4.700	0.030	3.731	1.135–12.270
History of smoking	0*						
	1	1.218	0.638	3.647	0.056	3.382	0.968–11.808
History of alcohol consumption	0*						
	1	−1.083	0.595	3.317	0.069	0.339	0.106–1.086
Fasting blood-glucose		0.100	0.233	0.184	0.668	1.105	0.699–1.747
Homocysteine concentration		−0.027	0.035	0.592	0.442	0.973	0.909–1.043
CC+ Hyperglycemia	0*						
	1	2.128	1.260	2.854	0.091	8.401	0.711–99.255
CT/TT+ Hyperglycemia	0*						
	1	0.118	0.810	0.021	0.884	1.125	0.230–5.510

Notes: Gender 0 represent male; 1 represent female. *Control group. 0 represent no; 1 represent yes.

Table 4 Logistic Regression Analysis of MACE in PCI Patients <75 years

	ItermS	B	SE	Wald	*P* value	Exp (B)	EXP (B) 95.0% CI
Gender	0*						
	1	0.559	0.591	0.897	0.344	1.750	0.550–5.568
Age		0.059	0.031	3.644	0.056	1.061	0.998–1.127
History of hypertension	0*						
	1	1.148	0.497	5.326	0.021	3.151	1.189–8.350
History of diabetes mellitus	0*						
	1	1.088	0.599	3.304	0.069	2.969	0.918–9.598
History of alcohol consumption	0*						
	1	−0.825	0.570	2.092	0.148	0.438	0.143–1.340
Fasting blood glucose		0.097	0.203	0.230	0.631	1.102	0.741–1.639
CC+ Normoglycaemia	0*						
	1	−1.915	0.842	5.178	0.023	0.147	0.028–0.767
CT/TT+ Hyperglycemia	0*						
	1	0.109	0.663	0.027	0.869	1.115	0.304–4.088

Notes: Gender 0 represent male; 1 represent female. *Control group. 0 represent no; 1 represent yes.

Discussion

In this study, we evaluated the effect of the ABCB1 C3435T gene polymorphism combined with hyperglycemia on the risk of MACE after clopidogrel therapy in patients with PCI. The results of the study showed that the T allele of the *ABCB1* C3435T gene was 55.1%, which was in general agreement with the previous findings that the T allele rate was 34–63% in Asians.[33] Age, *ABCB1* genotype, history of hypertension, and history of diabetes mellitus were independent risk factors for MACE after clopidogrel therapy in PCI patients with a normal metabolic phenotype of *CYP2C19*. In patients <75 years, the history of hypertension was an independent risk factor for MACE after clopidogrel therapy in PCI patients; Moreover, *ABCB1* (CC) combined normoglycemia was a protective factor for MACE after clopidogrel therapy in PCI patients.

The ABCB1 C3435T gene mutation can lead to an increase in p-glycoprotein activity, thereby reducing systemic exposure to clopidogrel and its active metabolites, ultimately affecting its clinical efficacy. Therefore, individuals carrying the ABCB1 C3435T mutation have a higher risk of ischemic events. Thus, individuals with *ABCB1* C3435T mutations are theoretically at reduced risk of ischaemic events, but may face an elevated risk of bleeding. In patients treated with clopidogrel, the *ABCB1* C3435T genotype was significantly associated with the risk of cardiovascular death, myocardial infarction, or stroke (P= 0.0064). Compared with CT/CC individuals, TT homozygotes had a 72% increased risk of MACE (HR 1.72, 95% CI 1.22–2.44, P= 0.002).[26] PLATO trial data showed that patients with *ABCB1* C3435T wild-type genotype had a higher rate of ischaemic events than patients with the mutant genotype, suggesting that those with the allelic mutation may have a higher rate of clopidogrel uptake and clinical outcome.[27] Additionally, it was found that AMI patients with TT and CT genotypes had a higher incidence of ischaemic events at 1 year compared to patients with CC wild-type genotype (15.5% vs 10.7%; adjusted HR 1.72; 95% CI 1.20–2.47).[34] However, the *ABCB1* C3435T genotype was not found to have any effect on the antiplatelet activity of clopidogrel and MACE, and there was no difference in the incidence of MACE among *ABCB1* C3435T genotypes (HR 0.8; 95% CI 0.3–1.9; P= 0.603).[28,35] Therefore, the *ABCB1* C3435T genotype cannot be used to personalize clopidogrel regimens for improved management of high risk patients.[36] These conflicting results may be influenced by factors such as *CYP2C19* gene polymorphisms, age, and blood glucose levels. The study confirmed that the incidence of MACE in patients with combined T2DM was approximately 117.46% and 29.68% at 30 days and 3 years after PCI, respectively.[37] Blood glucose levels affect the activity of the *ABCB1* encoded P-protein.[32] To minimize the influence of these factors on the study results, we chose patients with *CYP2C19* normal metabolism and considered factors such as combined hyperglycaemia with the *ABCB1* genotype. Our results showed that the proportion of *ABCB1*(CC) combined normoglycaemia was significantly higher in the normal group than in the MACE group, while the proportion of *ABCB1* (CT/TT) combined hyperglycaemia was significantly lower than in the MACE group. Multifactorial logistic regression analysis revealed that the *ABCB1* C3435T genotype was an independent risk factor for MACE after clopidogrel treatment in PCI patients (OR = 5.584; 95% CI 1.258–24.780; P= 0.024). However, no association was found between the combined *ABCB1* C3435T genotype with hyperglycemia and MACE. The study also revealed a significantly higher prevalence of CHD in the age group >75.[38] To reduce the influence of age on the trial results, we excluded patients >75 years and analysed the data. The study results showed that the *ABCB1*(CC) combined normoglycaemia was a protective factor for MACE after clopidogrel treatment in patients with PCI (P= 0.023; OR = 0.147; 95% CI 0.028–0.767). *ABCB1 C3435T* mutation can increase P-glycoprotein expression, leading to reduced intestinal absorption of clopidogrel. Hyperglycemia enhances P-glycoprotein phosphorylation by activating the PKC pathway, further reducing drug bioavailability, and this synergistic effect is more significant in patients under 75 years old. This study confirms for the first time in a population with normal CYP2C19 metabolism that the combination of the *ABCB1*(CC) genotype and normal blood glucose reduces the risk of MACE by 85%.

The limitations of this study include a small sample size from a single center and the fact that this relatively small sample size does not guarantee the statistical significance of the findings or adequately assess the influence of genetic factors. Therefore, it is necessary to expand the sample size and conduct experiments at multiple centers to reduce the bias of statistical results. Meanwhile, the distribution of *ABCB1* gene polymorphisms varies among races and geographic regions. Further experiments are still needed to verify the findings applicable to other ethnic groups.

Conclusion

This study confirms that the ABCB1 C3435T genotype is an independent risk factor for MACE in PCI patients on clopidogrel, particularly among those with comorbid hypertension or diabetes. In patients <75 years of age, the *ABCB1* (CC) combined normoglycaemia is a protective factor for MACE after clopidogrel therapy in PCI patients.

Data Sharing Statement

All datasets in this study can be obtained from the corresponding authors on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Affiliated Taian City Central Hospital of Qingdao University Ethics Committee of the institute (No. 2021-06-50, date: 11.05.2021), and all patients or their families gave informed consent.

Consent for Publication

All authors gave their consent for publication on this journal.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared no competing interests in this work.

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