Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Issue 2, Page No: 16-25

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Relationship of ABCB1 Genetic Variants with Post-PCI Clopidogrel Response: Links to Hyperglycemia and Major Adverse Cardiovascular Events (MACE)

Wei Chen[1]*, Li Zhang[1]

[1]Department of Clinical Pharmacy and Pharmacotherapy, Faculty of Pharmaceutical Sciences, Peking University, Beijing, China.

***E-mail** ✉ wei.chen@outlook.com

Received: 24 March 2025; **Revised:** 06 July 2025; **Accepted:** 08 July 2025

ABSTRACT

In patients undergoing PCI and treated with clopidogrel, we explored whether the combination of blood glucose status and ABCB1 C3435T genetic variation could help identify those at higher risk of developing major adverse cardiovascular events (MACE). A total of 117 patients were included in the analysis, among whom 52 experienced MACE. Genotyping of CYP2C19 and ABCB1 C3435T was performed using fluorescence-based in situ hybridization. Clinical data, including baseline characteristics, fasting glucose levels, and outcome events, were systematically collected. Logistic regression models were used to identify variables associated with MACE in patients receiving clopidogrel after PCI. When comparing patients with and without MACE, several baseline characteristics showed significant imbalance, including demographic factors (such as sex and age), metabolic and clinical history (diabetes, hypertension, alcohol use), fasting glucose levels, and genotype–glycemia combinations of ABCB1 C3435T. All of these differences reached statistical significance ($P < 0.05$). In the multivariate model, four variables independently contributed to MACE risk. The ABCB1 C3435T variant showed a strong association with adverse outcomes (OR = 5.584, P = 0.024). Increasing age was also associated with a higher risk (OR = 1.073 per unit increase, P = 0.014), as was a history of hypertension (OR = 3.144, P = 0.020) and diabetes mellitus (OR = 3.731, P = 0.030). In patients younger than 75 years, the pattern of associations changed slightly: hypertension remained a significant predictor of MACE (OR = 3.151, P = 0.021), while individuals carrying the ABCB1 CC genotype with normal glycemic status showed a significantly reduced risk, suggesting a protective effect in this subgroup (OR = 0.147, P = 0.023). The ABCB1 C3435T polymorphism appears to independently contribute to the risk of major adverse cardiovascular events in patients receiving clopidogrel after PCI. In contrast, the combination of the CC genotype with normal glycemic status may be associated with a reduced risk of MACE, particularly in individuals younger than 75 years.

Keywords: Major adverse cardiac events, PCI, Genetic polymorphism, *ABCB1* C3435T, Coronary artery disease

How to Cite This Article: Chen W, Zhang L. Relationship of ABCB1 Genetic Variants with Post-PCI Clopidogrel Response: Links to Hyperglycemia and Major Adverse Cardiovascular Events (MACE). Ann Pharm Pract Pharmacother. 2025;5(2):16-25. https://doi.org/10.51847/IFcjnehakU

Introduction

Coronary atherosclerotic heart disease (CHD) is a chronic cardiovascular condition caused by progressive atherosclerotic narrowing or obstruction of the coronary arteries, which ultimately leads to myocardial ischemia, hypoxia, or infarction [1]. In recent decades, CHD has shown a continuous rise in incidence and is now recognized as one of the leading causes of global mortality [2, 3]. In China, the disease burden remains substantial. In 2020, the reported CHD mortality rates were 126.91 per 100,000 in urban populations and 135.88 per 100,000 in rural regions, with a persistent upward trend observed between 2012 and 2020, particularly in rural areas. At present, the number of patients living with CHD in China is estimated to exceed 11 million [4]. Percutaneous coronary intervention (PCI) represents a key therapeutic strategy for CHD, significantly reducing the risk of major adverse cardiovascular events (MACE) [5]. MACE is generally defined as a composite endpoint that includes outcomes

such as cardiac death, myocardial infarction, stroke, stent thrombosis, urgent target vessel revascularization, repeat revascularization for non-emergent indications, unstable angina, atrial fibrillation, and ventricular fibrillation [6, 7]. Despite advances in interventional therapy, MACE may still occur during the months following PCI, with reported mortality rates exceeding 5% [8, 9]. Dual antiplatelet therapy (DAPT) remains the standard of care for secondary prevention after PCI and has been shown to significantly reduce the incidence of these adverse cardiovascular events [10, 11]. Clopidogrel, a key component of dual antiplatelet therapy (DAPT), is widely used after PCI; however, a considerable proportion of patients (approximately 4%–30%) exhibit reduced responsiveness or resistance to the drug [12]. The underlying causes of clopidogrel resistance remain incompletely understood. They are considered multifactorial, involving clinical characteristics such as age, smoking status, diabetes, hypertension, medication adherence, and drug–drug interactions, as well as genetic variability [13, 14]. As a prodrug, clopidogrel requires intestinal absorption followed by hepatic biotransformation to generate its active metabolite. Intestinal uptake is partly regulated by P-gp encoded by the ABCB1 gene [15], while hepatic activation depends mainly on enzymatic pathways involving CYP2C19 and, to a lesser extent, PON1 [16]. Among these, CYP2C19 is regarded as the principal determinant of antiplatelet response, and loss-of-function variants have been consistently linked to increased risk of adverse cardiovascular outcomes, including MACE [17–19]. The ABCB1 gene, a member of the ATP-binding cassette transporter family first identified in the 1970s [20], encodes P-glycoprotein, a transmembrane efflux transporter highly expressed in various tissues, including malignant cells [21]. This protein plays an important role in drug transport by facilitating the efflux of substrates from intracellular to extracellular compartments [22]. More than 50 ABCB1 variants have been described, among which C3435T, G2677T/A, and C1236T are the most extensively studied, with C3435T receiving the greatest research attention [23]. The C3435T variant is located in exon 26 and, although synonymous, has been associated with altered P-glycoprotein structure and function [24]. Evidence suggests that individuals carrying the TT genotype may exhibit increased intestinal ABCB1 mRNA expression compared with CC or CT carriers, potentially enhancing drug efflux [25]. Functionally, the T allele may reduce intestinal absorption of clopidogrel by increasing P-gp–mediated efflux, thereby decreasing systemic drug exposure and antiplatelet efficacy. Importantly, the frequency of ABCB1 polymorphisms varies across ethnic and geographic populations, which may contribute to inter-individual differences in drug response. Previous clinical studies have suggested that genetic variation in ABCB1, particularly the C3435T polymorphism, may be associated with variability in cardiovascular outcomes among patients receiving clopidogrel after acute coronary syndrome and PCI. Individuals carrying the TT genotype have been reported to experience a higher incidence of adverse cardiovascular events during antiplatelet therapy [26]. In addition, this variant has also been implicated in differences in bleeding risk following PCI, further indicating its potential influence on clopidogrel response [27]. Evidence regarding genotype-specific effects is not entirely consistent. While some studies report an increased risk of MACE in TT carriers after PCI, others have found no significant impact of the CT genotype on platelet inhibition or clinical outcomes [23, 28]. Overall, the relationship between the ABCB1 C3435T polymorphism and cardiovascular prognosis remains debated. Metabolic status may further modify P-glycoprotein function. In diabetic conditions, blood glucose levels have been shown to correlate positively with P-gp activity. However, the direction and magnitude of this effect may vary by tissue type and disease duration [29, 30]. Moreover, certain anti-diabetic medications may influence drug absorption by modulating P-gp activity, potentially affecting intestinal transport of co-administered therapies [31]. However, the current literature remains inconsistent regarding the overall impact of diabetes on ABCB1 expression and function [32]. Given these uncertainties, the present study was designed to investigate whether the combination of ABCB1 C3435T genetic variation and hyperglycemia is associated with the risk of major adverse cardiovascular events in patients treated with clopidogrel following PCI.

Materials and Methods

Study participants

Patients with coronary heart disease (CHD) who underwent percutaneous coronary intervention (PCI) at Taian Central Hospital between 1 June 2018 and 30 September 2021 were retrospectively identified and included in this study. All patients had CYP2C19 and ABCB1 C3435T genotyping performed during hospitalization. Follow-up was conducted at 1, 6, and 12 months after PCI through outpatient review and readmission records. The dataset was accessed for research analysis from 1 June 2018 to 30 September 2022. Patients were included if they were

older than 18 years, had a confirmed diagnosis of coronary artery disease according to the Diagnostic and Therapeutic Guidelines for Stable CHD, were CYP2C19 normal metabolizers, underwent first-time PCI, and received standard dual antiplatelet therapy consisting of clopidogrel (75 mg once daily) plus aspirin (100 mg once daily) for 12 months. Individuals were also required to have complete clinical data and to follow up until the occurrence of endpoint events. Exclusion criteria comprised malignant tumors, contraindications to antiplatelet therapy, bleeding disorders, severe dysfunction of major organs, and pregnancy or lactation. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Taian Central Hospital of Qingdao University (2020 Lunshen No. 60). Written informed consent was obtained from all participants or, in cases of reduced cognitive function (score ≤ 25), from their legal representatives.

Reagents and instruments

A range of laboratory materials and instruments were used in this study, including a commercial sequencing reaction system and nucleic acid extraction reagents. Standard laboratory chemicals, such as ammonium chloride (NH_4Cl), and sterile water for injection (500 mL) were also used. Molecular analysis was performed using a TL998A fluorescence detection system. Sample processing and centrifugation were performed using an Eppendorf 5418 high-speed centrifuge and 1.5 mL microcentrifuge tubes. Pipetting was performed using calibrated Eppendorf micropipettes (10 μL, 200 μL, and 1000 μL) together with matching sterile pipette tips. Blood samples were collected in 2 mL EDTA anticoagulation tubes.

Experimental methods

Specimen collection

A total of 1.5 mL of peripheral venous blood was drawn from each patient into EDTA anticoagulant tubes. Samples were gently inverted to ensure adequate mixing and to avoid hemolysis or clot formation, then temporarily stored at 4°C for no longer than 24 hours. For long-term storage, specimens were subsequently transferred and preserved at −20°C until further analysis.

ABCB1 genotyping procedure

Genomic DNA was obtained using a stepwise processing protocol. First, 150 μL of whole blood was added to a centrifuge tube containing 1 mL of ammonium chloride solution, and the mixture was incubated for 5 minutes. The sample was then centrifuged at 3000 rpm for 5 minutes, after which the supernatant was carefully removed. Next, 50 μL of nucleic acid purification reagent was added to the pellet and thoroughly mixed. A 1.5 μL aliquot of the resulting suspension was then transferred into the corresponding wells of a universal sequencing reaction kit. Pipetting was performed carefully to ensure no residual liquid remained in the tip, and the reaction tubes were securely sealed. Samples were gently inverted several times, briefly tapped to remove air bubbles, and then spun briefly in a microcentrifuge to collect any liquid from the tube walls. The prepared mixtures were then loaded into the designated system according to sample identifiers. Fluorescence-based detection was performed using a TL998A fluorescence analyzer, and the resulting fluorescence signal patterns were analyzed to determine ABCB1 genotypes.

Clinical data collection

Data collection included baseline demographic and clinical information such as age, sex, smoking and alcohol history, hypertension and diabetes status, ABCB1 genotype, fasting glucose, and homocysteine measurements obtained either at the time of event occurrence or at the 12-month assessment point. Patients were prospectively followed after discharge at 1, 6, and 12 months, using both outpatient review and hospital readmission records to ensure complete follow-up. The endpoint of interest during the follow-up period was the development of major adverse cardiovascular events (MACE).

Statistical analysis

The Hardy–Weinberg equilibrium test was performed to assess whether the genotype distribution of the study population was representative. All statistical analyses were conducted using SPSS version 25.0. Continuous variables with a normal distribution were summarized as mean ± standard deviation and compared between groups using independent-samples t-tests. For variables that did not conform to normality, data were described as median with interquartile range [M (P25, P75)], and group comparisons were performed using the Mann–Whitney U test

(rank-sum test). Categorical variables were expressed as frequencies and percentages, and differences between groups were evaluated using the chi-square test. Univariate and multivariate logistic regression analyses were performed to identify factors associated with MACE in patients undergoing PCI. A P-value < 0.05 was considered statistically significant.

Results and Discussion

HWE equilibrium test

The Hardy–Weinberg equilibrium test for the ABCB1 C3435T polymorphism was conducted in 117 patients with coronary heart disease. The results showed no significant deviation from equilibrium (P > 0.05), indicating that the genotype distribution in the study cohort was consistent with Hardy–Weinberg expectations and suggesting that the sampled population was well represented **(Table 1).**

Table 1. Hardy–Weinberg equilibrium analysis of ABCB1 C3435T genotypes.

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 genotype; CT = heterozygous genotype; TT = mutant homozygous genotype.

Patients' baseline characteristics

Among the 117 enrolled patients, 52 experienced MACE, corresponding to an incidence of 44.4%. Baseline comparison between the MACE and non-MACE groups showed no significant differences in hypertension history, smoking status, homocysteine levels, ABCB1 CC genotype with hyperglycemia, or ABCB1 CT/TT genotype with normoglycemia (P > 0.05). In contrast, significant differences were observed for sex, age, diabetes history, alcohol consumption, fasting blood glucose, ABCB1 CC combined with normoglycemia, and ABCB1 CT/TT combined with hyperglycemia (P < 0.05). The detailed baseline characteristics are presented in **Table 2.**

Table 2. Baseline characteristics.

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

Genotype distribution

The ABCB1 C3435T polymorphism was identified using fluorescence-based detection, as illustrated in **Figure 1.** The frequency of the T allele was 53.1% in one group and 57.7% in the other group.

Comparison of genotype distribution and allele frequencies between the two groups revealed no statistically significant differences (P > 0.05), as shown in **Figure 2.**

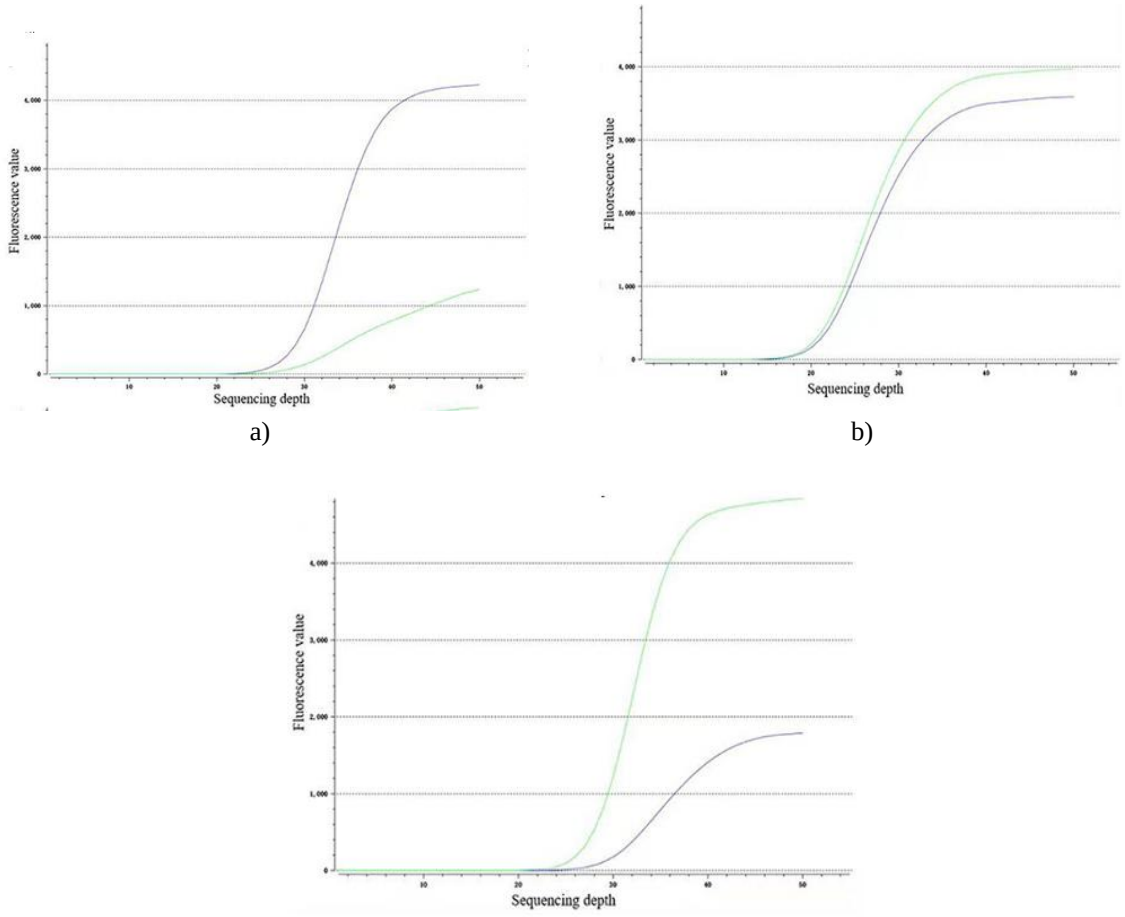

Figure 1. Sequencing chromatograms illustrating ABCB1 C3435T genotypes. (a) CC homozygous wild-type, (b) CT heterozygous, and (c) TT homozygous mutant.

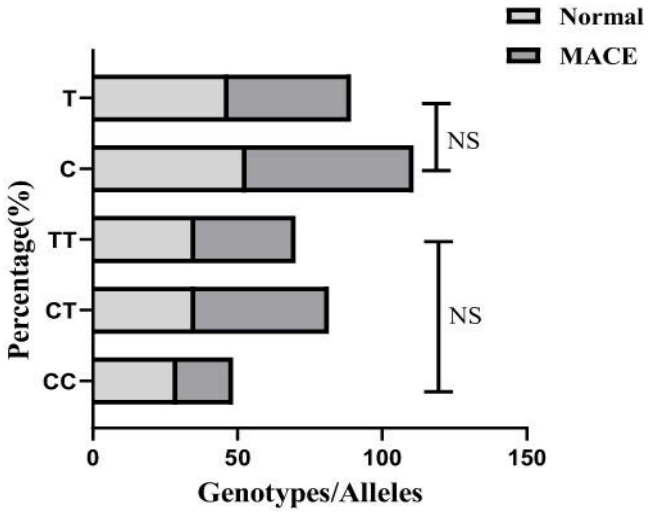

Figure 2. Comparison of ABCB1 C3435T genotype distribution between the non-MACE (normal) group and the MACE group.

A multivariable logistic regression approach was applied to identify determinants of MACE following clopidogrel therapy in patients undergoing PCI

MACE was defined as the dependent outcome variable. At the same time, demographic characteristics, clinical history, laboratory indicators, and genetic factors—including sex, age, ABCB1 C3435T genotype, hypertension, diabetes mellitus, smoking, alcohol consumption, fasting blood glucose, homocysteine, and genotype–glycemia

interaction—were entered as explanatory variables. After adjustment for covariates, four factors remained statistically significant. The ABCB1 C3435T polymorphism showed a strong association with MACE risk (OR = 5.584, P = 0.024), followed by age (OR = 1.073, P = 0.014), hypertension history (OR = 3.144, P = 0.020), and diabetes mellitus (OR = 3.731, P = 0.030). These findings are summarized in **Table 3.**

Table 3. Multivariate logistic regression analysis of MACE in PCI patients.

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

Notes: Gender coded as 0 = male and 1 = female. *Reference (control) category. For clinical history variables, 0 indicates absence, and 1 indicates presence.

Multivariable logistic regression analysis of determinants of MACE in PCI Patients younger than 75 years receiving clopidogrel therapy

Patients aged 75 years or older were excluded from this subgroup analysis. A total of 108 participants were included for evaluation. Initially, univariate logistic regression was performed, and variables with P < 0.1 were subsequently entered into a multivariable model for further analysis. The results indicated that a history of hypertension was independently associated with an increased risk of MACE following clopidogrel therapy after PCI (OR = 3.151, 95% CI: 1.189–8.350; P = 0.021). In contrast, the combination of the ABCB1 CC genotype with normal glycemic status was identified as a protective factor against MACE (OR = 0.147, 95% CI: 0.028–0.767; P = 0.023). These findings are summarized in **Table 4.**

Table 4. Logistic regression analysis of MACE risk in PCI patients aged < 75 years.

	ItermS	EXP (B) 95.0% CI	Exp (B)	*P* value	Wald	SE	B
Gender	0*						
	1	0.550–5.568	1.750	0.344	0.897	0.591	0.559
Age		0.998–1.127	1.061	0.056	3.644	0.031	0.059
Prior history of hypertension	0*						
	1	1.189–8.350	3.151	0.021	5.326	0.497	1.148
Medical history of diabetes mellitus	0*						
	1	0.918–9.598	2.969	0.069	3.304	0.599	1.088
Alcohol use history	0*						
	1	0.143–1.340	0.438	0.148	2.092	0.570	−0.825

Fasting blood glucose level		0.741–1.639	1.102	0.631	0.230	0.203	0.097
CC+ Normoglycaemia level	0*						
	1	0.028–0.767	0.147	0.023	5.178	0.842	−1.915
CT/TT+ Hyperglycemia level	0*						
	1	0.304–4.088	1.115	0.869	0.027	0.663	0.109

Notes: Gender was coded as 0 = male and 1 = female. *Reference category (control group). For binary variables, 0 indicates absence, and 1 indicates the presence of the condition.

This work examined the combined impact of the ABCB1 C3435T genetic polymorphism and elevated blood glucose on MACE occurrence following clopidogrel treatment in patients who underwent PCI. Our analysis revealed a T allele prevalence of 55.1% for the ABCB1 C3435T variant, a figure that corresponds generally with previously published T allele frequencies of 34–63% among Asian cohorts [33]. Age, ABCB1 carrier status, a clinical background of hypertension, and a diabetes diagnosis were identified as independent contributors to MACE after clopidogrel administration in PCI-treated individuals exhibiting a normal CYP2C19 metabolic profile. Among those below 75 years, a hypertensive history independently predicted MACE post-clopidogrel therapy following PCI. Moreover, possessing the ABCB1 (CC) genotype in the setting of normal blood glucose was protective against MACE in this therapeutic scenario.

The ABCB1 C3435T mutation can drive enhanced P-glycoprotein activity, thereby limiting systemic exposure to clopidogrel and its active metabolite and ultimately blunting clinical antiplatelet efficacy. As a consequence, carriers of the ABCB1 C3435T variant are theoretically at diminished risk for ischemic events but may instead be predisposed to a greater bleeding hazard. Among clopidogrel recipients, the ABCB1 C3435T genotype showed a strong relationship with the composite endpoint of cardiovascular mortality, myocardial infarction, or stroke (P = 0.0064). When compared with CT/CC individuals, TT homozygotes demonstrated a 72% increase in MACE risk (HR 1.72, 95% CI 1.22–2.44, P = 0.002) [26]. Evidence from the PLATO dataset indicated that those carrying the ABCB1 C3435T wild-type allele actually suffered more ischemic events than mutation carriers, hinting that allelic variants might facilitate greater clopidogrel bioavailability and more favorable clinical trajectories [27]. Complementing this, another report noted that AMI patients with TT and CT genotypes had a higher one-year ischemic event rate than CC wild-type subjects (15.5% vs 10.7%; adjusted HR 1.72; 95% CI 1.20–2.47) [34]. Conversely, some investigations failed to uncover any meaningful impact of the ABCB1 C3435T variant on clopidogrel-induced platelet inhibition or MACE rates, with no discernible divergence in MACE incidence across genotype strata (HR 0.8; 95% CI 0.3–1.9; P = 0.603) [28, 35]. Hence, the ABCB1 C3435T genotype, taken alone, is insufficient to guide personalized clopidogrel prescribing for improved management of high-risk populations [36]. These contradictory findings likely reflect the modulating influence of factors such as CYP2C19 genetic background, age, and glycemic status. It has been established that the rate of MACE among patients with comorbid T2DM approximates 117.46% at 30 days and 29.68% at 3 years following PCI [37]. Circulating glucose concentrations are known to affect the functional activity of the ABCB1-encoded P-glycoprotein [32]. To reduce confounding from these sources, we restricted our cohort to individuals with normal CYP2C19 metabolism and accounted for concomitant hyperglycemia and ABCB1 genotype. Our data demonstrated that the proportion of patients with the ABCB1 (CC) genotype and normoglycemia was appreciably higher in the event-free group than in the MACE group.

In contrast, the proportion with ABCB1 (CT/TT) and hyperglycemia was substantially lower in the event-free group. Multivariable logistic regression established the ABCB1 C3435T genotype as an independent risk determinant for MACE following clopidogrel therapy in PCI patients (OR = 5.584; 95% CI 1.258–24.780; P = 0.024). That said, the combination of ABCB1 C3435T genotype and hyperglycemia did not exhibit a significant association with MACE. Our analysis also brought to light a markedly higher CHD burden in the over-75 age bracket [38]. To reduce the confounding effect of advanced age, we excluded subjects aged 75 or older and conducted a subgroup analysis. The results from this refined dataset showed that the combination of ABCB1 (CC) and normoglycemia was a protective factor against MACE after clopidogrel treatment in PCI patients (P = 0.023; OR = 0.147; 95% CI 0.028–0.767). The ABCB1 C3435T mutation can upregulate P-glycoprotein expression, leading to decreased intestinal absorption of clopidogrel. Hyperglycemia, through PKC-mediated enhancement of P-gp phosphorylation, further depresses drug bioavailability—an interaction that appears particularly consequential in individuals younger than 75 years. This investigation provides the first demonstration, within a

cohort with unimpaired CYP2C19 metabolism, that the concurrent presence of the ABCB1 (CC) genotype and euglycemia reduces MACE risk by 85%.

Several limitations warrant acknowledgment, including the modest patient numbers from a single center, which limit statistical robustness and hinder a comprehensive appraisal of genetic contributions. Future efforts should therefore encompass larger sample sizes and multicenter designs to mitigate statistical bias. Additionally, the distribution of ABCB1 polymorphisms differs across ethnicities and geographic regions, suggesting that confirmatory studies in other populations will be necessary to extend the generalizability of these results.

Conclusion

This study suggests that the ABCB1 C3435T polymorphism is independently associated with the risk of MACE in PCI patients receiving clopidogrel, especially in those with concomitant hypertension or diabetes. In patients younger than 75 years, the combination of the ABCB1 CC genotype and normal glycemic status appears to be associated with a reduced risk of MACE following PCI with clopidogrel.

Acknowledgments: We would like to express our sincere gratitude to all authors for their valuable contributions to this work.

Conflict of Interest: None

Financial Support: This study was supported by the Taian Science and Technology Development Project (Grant Nos. 2020NS141, 2021NS372, and 2023NS440).

Ethics Statement: This study was reviewed and approved by the Ethics Committee of the Affiliated Taian Central Hospital of Qingdao University (Approval No. 2021-06-50; approval date: 11 May 2021). Written informed consent was obtained from all participants or, where applicable, from their legal family representatives before inclusion in the study.

All authors have read and approved the final manuscript and consent to its publication in this journal.

References

1. Wu AD, Liu JK, Zhao Y, Wang H, Chen X, Li Q, et al. Genetics of coronary artery disease. Sci Sin. 2022;52(2):123-37.
2. Yu L, Li Z, Yang R, Wang Y, Chen H, Zhao X, et al. Impaired sensitivity to thyroid hormones is associated with elevated blood glucose in coronary heart disease. Front Endocrinol. 2022;13.
3. Ding J, Wu J, Wei H, Zhang Y, Liu X, Chen Q, et al. Exploring the mechanism of Hawthorn leaves against coronary heart disease using network pharmacology and molecular docking. Front Cardiovasc Med. 2022;9.
4. Writing Committee of the Report on Cardiovascular Health and Diseases in China. Report on cardiovascular health and diseases in China 2022: an updated summary. Chin Circ J. 2023;38(6):583-612.
5. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization. J Am Coll Cardiol. 2022;79(2):e21-129.
6. Nicholls SJ, Bhatt DL, Buse JB, Cornel JH, Diaz R, Heerspink HJL, et al. Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. Am Heart J. 2024;267:1-11.
7. Robinson CH, Hussain J, Jeyakumar N, O'Brien E, Patel N, Singh A, et al. Long-term cardiovascular outcomes in children and adolescents with hypertension. JAMA Pediatr. 2024;178(7):688.
8. Yang MS, Li SHC, Geng CHQ, Wang YL, Zhao HY, Liu JQ, et al. Advances in in-stent restenosis after percutaneous coronary intervention. Chin J Integr Med Cardio-Cerebrovasc Dis. 2023;21(20):3754-60.
9. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, et al. Effect of Alirocumab on Lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol. 2020;75(2):133-44.
10. Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Guidelines for the diagnosis and treatment of acute ST-segment elevation myocardial infarction (2019). Chin J Cardiol. 2019;47(10):766-83.

11. Pan MM. Influencing Factors of Clopidogrel Efficacy and the Effect of PON1 Gene Polymorphism on MACE Risk [thesis]. Shanghai: Shanghai Jiao Tong University; 2020.
12. Musallam A, Orvin K, Perl L, Roguin A, Banai S, Vaknin-Assa H, et al. Effect of modifying antiplatelet treatment to ticagrelor in high-risk coronary patients with low response to clopidogrel (MATTIS). Can J Cardiol. 2016;32(10):1246.e13-19.
13. Hurst NL, Nooney VB, Raman B, Chirkov YY, De Caterina R, Horowitz JD. Clopidogrel "resistance": pre- vs post-receptor determinants. Vasc Pharmacol. 2013;59(5-6):152-61.
14. Hong DZH, He ZHL, Zeng SHQ, Liu XY, Wang JP, Chen YL, et al. Correlation of CYP2C19 gene polymorphism and stent restenosis rate with clopidogrel efficacy in patients undergoing coronary stenting. Chin J Integr Med Cardio-Cerebrovasc Dis. 2023;21(18):3426-30.
15. Ishiyama H, Okazaki S, Saito K, Yamagami H, Ihara M. Rolling stones sign as hard and fast evidence of calcified cerebral emboli. Neurology. 2018;91(1):41-3.
16. Zhang Z, Chen M, Zhang L, Zhao Q. The impact of cytochrome 450 and Paraoxonase polymorphisms on clopidogrel resistance and major adverse cardiac events in coronary heart disease patients after percutaneous coronary intervention. BMC Pharmacol Toxicol. 2020;21(1).
17. Zhang YY, Zhou X, Ji WJ, Shi DM, Yang YJ, Li YM, et al. Association between CYP2C19*2/*3 polymorphisms and coronary heart disease. Curr Med Sci. 2019;39(1):44-51.
18. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther. 2022;112(5):959-67.
19. Baudhuin LM, Train LJ, Goodman SG, Paré G, Tanguay JF, Welsh RC, et al. Point of care CYP2C19 genotyping after percutaneous coronary intervention. Pharmacogenomics J. 2022;22(5-6):303-7.
20. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta. 1976;455(1):152-62.
21. Ambudkar SV, Lelong IH, Zhang J, Cardarelli C. Purification and reconstitution of human P-glycoprotein. Methods Enzymol. 1998;292:492-504.
22. Dong J, Yuan L, Hu C, Cheng X, Qin JJ. Strategies to overcome cancer multidrug resistance (MDR) through targeting P-glycoprotein (ABCB1): an updated review. Pharmacol Ther. 2023;249:108488.
23. Biswas M, Rahaman S, Biswas TK, Ibrahim B. Effects of the ABCB1 C3435T single nucleotide polymorphism on major adverse cardiovascular events in acute coronary syndrome or coronary artery disease patients undergoing percutaneous coronary intervention and treated with clopidogrel: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020;19(12):1605-16.
24. Amin ML. P-glycoprotein inhibition for optimal drug delivery. Drug Target Insights. 2013;7:27-34.
25. Taubert D, Von Beckerath N, Grimberg G, Lazar A, Jung N, Goeser T, et al. Impact of P-glycoprotein on clopidogrel absorption. Clin Pharmacol Ther. 2006;80(5):486-501.
26. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet. 2010;376(9749):1312-9.
27. Zhang JH, Tang XF, Zhang Y, Jin C, Song Y, Qiao SB, et al. Relationship between ABCB1 polymorphisms, thromboelastography and risk of bleeding events in clopidogrel-treated patients with ST-elevation myocardial infarction. Thromb Res. 2014;134(5):970-5.
28. Jeong YH, Tantry US, Kim IS, Hwang SJ, Park Y, Koh JS, et al. Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in east asian acute myocardial infarction survivors treated with clopidogrel and aspirin. Circ Cardiovasc Interv. 2011;4(6):585-94.
29. Neyshaburinezhad N, Rouini M, Shirzad N, Gholami K, Asadipooya K, Nili-Ahmadabadi A, et al. Evaluating the effect of type 2 diabetes mellitus on CYP450 enzymes and P-gp activities, before and after glycemic control: a protocol for a case-control pharmacokinetic study. MethodsX. 2020;7:100853.
30. Zhang LL, Lu L, Jin S, Jing XY, Yao D, Hu N, et al. Tissue-specific alterations in expression and function of P-glycoprotein in streptozotocin-induced diabetic rats. Acta Pharmacol Sin. 2011;32(7):956-66.
31. Abbasi MM, Valizadeh H, Hamishehkar H, Zakeri-Milani P. Inhibition of P-glycoprotein expression and function by anti-diabetic drugs gliclazide, metformin, and pioglitazone in vitro and in situ. Res Pharm Sci. 2016;11(3):177-86.

32. Gravel S, Panzini B, Belanger F, Turgeon J, Michaud V. A pilot study towards the impact of type 2 diabetes on the expression and activities of drug metabolizing enzymes and transporters in human duodenum. Int J Mol Sci. 2019;20(13):3257.
33. Petryszyn P, Dudkowiak R, Gruca A, Wisniewska-Jarosinska M, Najda J, Malecka-Panas E, et al. C3435T polymorphism of the ABCB1 gene in Polish patients with inflammatory bowel disease: a case-control and meta-analysis study. Genes. 2021;12(9):1419.
34. Simon T, Bhatt DL, Bergougnan L, Farenc C, Pearson K, Perrin L, et al. Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. Clin Pharmacol Ther. 2011;90(2):287-95.
35. Mugosa S, Todorovic Z, Cukic J, Sahman-Zaimovic M, Djordjevic N. ABCB1 polymorphism in clopidogrel-treated Montenegrin patients. Open Life Sci. 2021;16(1):142-9.
36. Samardzic J, Bozina N, Skoric B, Lucijanic T, Vrsalovic M, Pejkovic B, et al. Impact of continuous P2Y12 inhibition tailoring in acute coronary syndrome and genetically impaired clopidogrel absorption. J Cardiovasc Pharmacol. 2020;75(2):174-9.
37. Różycka-Kosmalska M, Kosmalski M, Wranicz JK. Impact of admission glycaemia on the annual risk of major cardiovascular events and development of type 2 diabetes mellitus in patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention. Pol Merkur Lekarski. 2019;47(282):207-11.
38. Damluji AA, Forman DE, Wang TY, Chikwe J, Kunadian V, Rich MW, et al. Management of acute coronary syndrome in the older adult population: a scientific statement from the American Heart Association. Circulation. 2023;147(3).