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The relationship between ABO blood types and clopidogrel-related low on-treatment platelet reactivity in patients with coronary artery diseases and type 2 diabetes mellitus: a secondary analysis of a prospective cohort study

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Abstract

Background The risk of bleeding associated with antiplatelet therapy in patients with coronary artery disease (CAD) has received a lot of attention. The aim of this study was to investigate the relationship between ABO blood system and low on-treatment platelet reactivity (LTPR) in patients with CAD and type 2 diabetes mellitus (T2DM).

Methods This study examined 10,724 consecutive patients who received percutaneous coronary intervention in China between January and December in 2013 and applied logistic regression to assess the association between ABO blood types and LTPR. These patients who were diagnosed with T2DM, had thromboelastogram (TEG) results and were administered clopidogrel were ultimately enrolled. LTPR is defined by a platelet maximum amplitude of < 31 mm on TEG, induced by adenosine diphosphate.

Results Among 3,039 patients (mean age, 59.35 ± 9.89; male, 74.60%), 1,089 (35.83%) presented with LTPR. Multivariate logistic regression revealed that blood type O was independently related to higher odds of LTPR (OR $_{\text{O vs. Non–O}}$: 1.298, 95% CI 1.099–1.534) and that blood type A was independently related to lower odds of LTPR (OR $_{\text{A vs. Non–A}}$: 0.804, 95% CI 0.674–0.958). For further analysis, multivariate logistic regression revealed that, compared to blood type A, type O was independently related to higher odds of LTPR (OR $_{\text{O vs. A}}$: 1.409, 95% CI 1.147–1.729).

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Conclusions This study reported that in patients with CAD and T2DM, blood type O was independently associated with higher odds of LTPR, indicating a greater likelihood of bleeding, while blood type A was independently related to lower odds of LTPR, suggesting a reduced likelihood of bleeding.

Keywords Platelet function tests, ABO blood-group system, Percutaneous coronary intervention, Diabetes mellitus, Bleeding

Background

There is a close relationship between type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD), both of which are becoming increasingly prevalent [1]. Patients with both CAD and T2DM are typically associated with worse clinical outcomes [2]. Previous studies indicated that CAD patients with T2DM have higher odds of bleeding complications, which are strongly linked to increased mortality [3, 4]. Therefore, identifying risk factors and understanding the mechanisms underlying the high bleeding risk in CAD patients with comorbid T2DM is crucial. Platelet reactivity is considered a key factor in assessing the likelihood of hemostasis and thrombosis, with notable variability among CAD patients treated with clopidogrel [5]. Low on-treatment platelet reactivity (LTPR) has been identified as a factor which could cause higher risk of bleeding for patients [6]. Clopidogrel-related platelet reactivity is affected by several factors, such as genetic and nongenetic determinants such as drug interactions, comorbidities, and age. However, the precise determinants in CAD patients with T2DM remain unclear [7].

Everyone has an ABO blood type, which has emerged as an important factor in various diseases, including cardiovascular diseases, cancer and hematologic disorders [8]. Studies suggested that blood type O patients may have prolonged bleeding times and were more prone to bleeding [9]. Another systematic review revealed that blood type O patients had a small but significantly increased risk of bleeding events, including gastrointestinal, intracranial, mucosal bleeding, and other complications [10, 11]. However, the association between ABO blood types and clopidogrel-related platelet reactivity has been studied in few studies.

This study demonstrated the influence of ABO blood types on clopidogrel-related platelet reactivity in a large group of patients with T2DM undergoing percutaneous coronary intervention (PCI). These findings may offer valuable mechanistic insights and inform future clinical application.

Methods

Study population

A total of 10,724 patients undergoing PCI at Fu Wai Hospital from January to December in 2013 were included in this prospective, single-center, observational study. Of these, TEG test results were available for 6,784 patients. According to the Guidelines for the Prevention and Treatment of Diabetes in China, T2DM was defined as follows [12]. After selecting patients with T2DM and excluding those treated with ticagrelor or missing ABO blood type data, the study eventually enrolled a total of 3,039 patients (Fig. 1).

All participants were administered aspirin and clopidogrel before PCI. Those who were not on antiplatelet therapy prior to the procedure were given a loading dose of 300 mg of aspirin and 300 to 600 mg of clopidogrel. Written informed consent was provided by each participant before the study, and the study protocol was approved by the Ethics Committee of Fuwai Hospital (approval number: 2013 – 449).

Laboratory measurements

Within 24 h of admission, blood samples were taken from all patients after an overnight fast. Biochemical markers, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), glucose, and estimated glomerular filtration rate (eGFR), were measured using an automated biochemical analyzer (LABOSPECT 008, HITACHI, Japan). Leukocyte count and hemoglobin levels were determined with a Sysmex XN 2000 automated blood cell counter (Sysmex Corporation, Kobe, Japan). ABO blood type was determined using standard agglutination techniques.

Platelet reactivity determination and definition

Platelet reactivity was assessed using adenosine diphosphate-induced maximum amplitude via thromboelastogram (TEG), which reflects clot strength after P2Y12 receptor antagonist administration. Venous blood samples were taken from patients in the supine position on the morning after PCI for the point-of-care TEG analysis. TEG parameters were measured using the TEG@5,000 thromboelastograph hemostasis system (American Hemoscope Corporation). Based on established definitions, LTPR is defined by a platelet maximum amplitude of < 31 mm on TEG, induced by adenosine diphosphate [13].

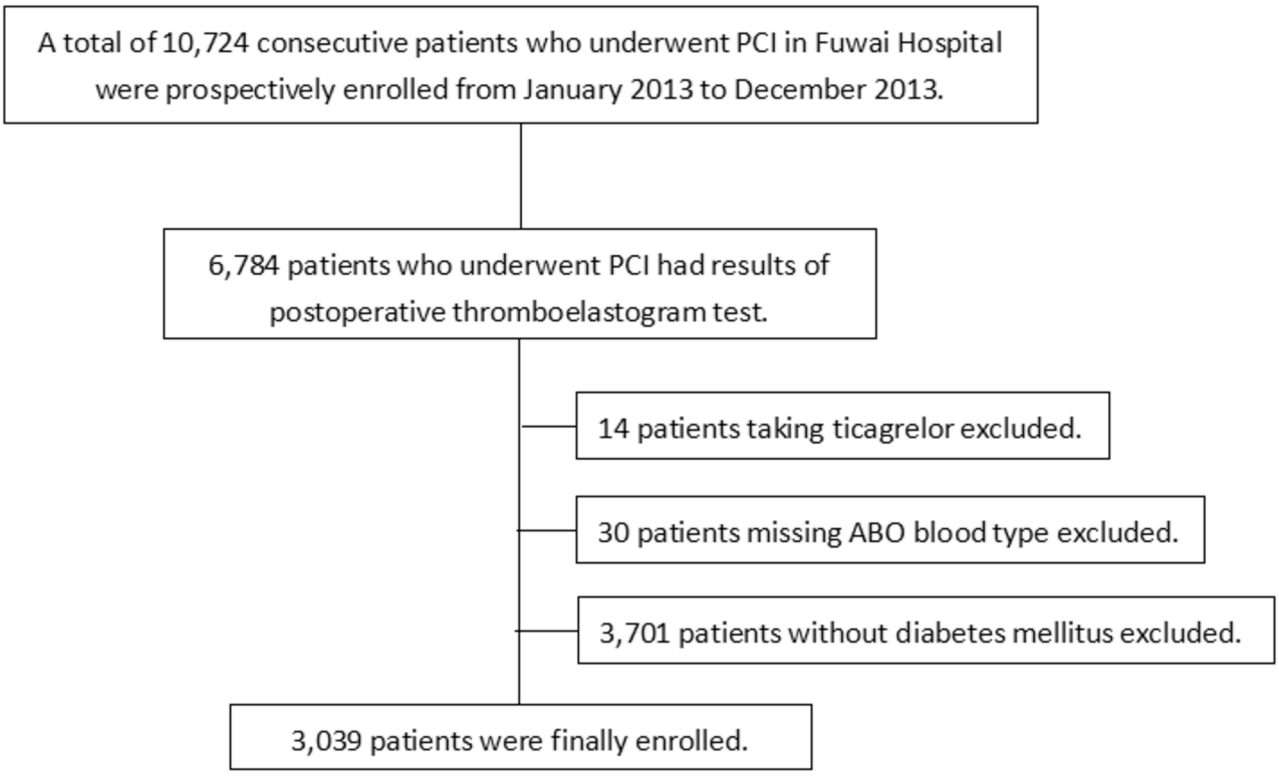

Fig. 1 Study flow chart. PCI, percutaneous coronary intervention

Statistical analysis

All Continuous variables are presented as mean ± standard deviation for data because of the normal distribution, while categorical variables are presented as frequencies (percentages). The independent t-test or Wilcoxon test compared continuous variables, and the Chi-square or Fisher's exact test was chosen to compare these categorical variables between the LTPR and non-LTPR groups.

Univariate logistic regression was used to identify factors related to LTPR. Based on significant variables from the univariate analysis, multivariate logistic regression was performed to assess the association between ABO blood types and LTPR. The impact of ABO blood types on LTPR across different subgroups was evaluated using multivariate logistic regression with tests for interaction. Statistical significance was defined as a two-sided *P* value < 0.05. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

In total, 3,039 PCI patients with comorbid T2DM (mean age 59.35 ± 9.89 years; 74.60% male) treated with clopidogrel were included in the analysis. The average adenosine diphosphate-induced maximum amplitude (MA(ADP)) measured by TEG was 37.00 ± 17.81 mm. Based on the MA(ADP) values, 1,089 (35.83%) patients presented LTPR, while 1,950 (64.17%) presented non-LTPR. The ABO blood type distribution was as follows: 896 (29.48%) type O, 834 (27.44%) type A, 999 (32.87%) type B, and 310 (10.20%) type AB.

There were statistically significant differences in sex, age, MA(ADP), smoking history, acute coronary syndrome (ACS), hypertension, prior myocardial infarction (MI), prior PCI, hemoglobin (HB), platelet count (PLT), LDL-C, TC, eGFR, O/non-O, A/non-A, and blood model between the LTPR and non-LTPR (all $P < 0.05$). For other indicators, there were no significant differences (all $P > 0.05$) (Table 1).

Relationship between ABO blood types and LTPR

A total of 357 (32.78%) patients with blood type O, 261 (23.97%) with type A, 364 (33.43%) with type B, and 107 (9.83%) with type AB presented with LTPR. In the O/non-O model, after adjusting for significant variables identified in the univariate analysis (Table 2), the multivariate logistic regression model showed that blood type O was independently related to LTPR (adjusted $OR_{O\ vs.\ non-O}$: 1.298, 95% CI 1.099–1.534, P = 0.002). Additionally, HB, PLT, and ACS were also independently associated with LTPR (all $P < 0.05$) (Table 3).

Table 1 Baseline characteristics of patients according to platelet reactivity

Parameter	LTPR (*N* = 1089)	Non-LTPR (*N* = 1950)	*P*-value
Sex [male, n(%)]	898 (82.46)	1369 (70.21)	< 0.001
Age, year	58.574 ± 9.723	59.787 ± 9.966	0.001
BMI, kg/m^2	26.288 ± 3.345	26.369 ± 3.044	0.493
MA(ADP), mm	16.878 ± 9.065	48.242 ± 9.803	< 0.001
Smoking history, *n* (%)	681 (62.53)	1042 (53.44)	< 0.001
ACS, *n* (%)	557 (51.15)	1119 (57.38)	< 0.001
Hyperlipidemia, *n* (%)	787 (72.27)	1437 (73.69)	0.396
Hypertension, *n* (%)	735 (67.49)	1399 (71.74)	0.014
COPD, *n* (%)	25 (2.30)	37 (1.90)	0.457
Family history of CHD, *n* (%)	268 (24.61)	474 (24.31)	0.842
Cerebrovascular disease history, *n* (%)	125 (11.48)	250 (12.82)	0.281
Peripheral vascular disease, *n* (%)	46 (4.22)	68 (3.49)	0.305
Prior myocardial infarction, *n* (%)	257 (23.60)	388 (19.90)	0.017
Prior PCI, *n* (%)	336 (30.85)	517 (26.51)	0.011
Prior CABG, *n* (%)	58 (5.33)	94 (4.82)	0.540
LVEF, %	62.657 ± 7.261	62.467 ± 7.439	0.496
Hemoglobin, g/L	146.271 ± 14.677	139.650 ± 15.459	< 0.001
PLT, 10^9/L	198.386 ± 55.648	207.777 ± 56.909	< 0.001
MPV, fL	10.687 ± 0.929	10.658 ± 0.938	0.417
LDL-C, mmol/L	2.385 ± 0.866	2.521 ± 0.915	< 0.001
HDL-C, mmol/L	1.017 ± 0.266	1.012 ± 0.263	0.597
TC, mmol/L	4.089 ± 1.040	4.245 ± 1.117	< 0.001
Triglyceride, mmol/L	1.852 ± 1.183	1.868 ± 1.163	0.713
Glucose, mmol/L	7.150 ± 2.243	7.303 ± 2.417	0.085
Glycosylated hemoglobin, %	7.436 ± 1.221	7.521 ± 1.312	0.078
eGFR, ml/min	91.235 ± 15.025	90.048 ± 15.787	0.043
The duration of DM, year	7.876 ± 6.234	8.082 ± 6.159	0.484
Use of hypoglycemic drugs, *n* (%)	555 (50.96)	1041 (53.38)	0.547
The type of drugs			
Insulin, *n* (%)	234 (21.49)	483 (24.77)	0.169
Metformin, *n* (%)	205 (18.82)	354 (18.15)	0.177
Alpha-glucosidase inhibitors, *n* (%)	151 (13.87)	268 (13.74)	0.427
Sulfonylureas, *n* (%)	104 (9.55)	164 (8.41)	0.102
Non-sulfonylurea insulin secretagogues, *n* (%)	46 (4.22)	85 (4.36)	0.863
Thiazolidinediones, *n* (%)	8 (0.76)	9 (0.46)	0.271
Blood model, *n* (%)			<0.001
O	357 (32.78)	539 (27.60)	
A	261 (23.97)	203 (10.40)	
B	364 (33.43)	635 (32.60)	
AB	107 (9.83)	203 (10.40)	
O/non-O model, *n* (%)			0.003
O	357 (32.78)	539 (27.64)	
Non-O	732 (67.22)	1411 (72.36)	
A/non-A model, *n* (%)			0.001
A	261 (23.97)	573 (29.38)	
Non-A	828 (76.03)	1377 (70.62)	
B/non-B model, *n* (%)			0.628
B	364 (33.43)	635 (32.56)	
Non-B	725 (66.57)	1315 (67.44)	
AB/non-AB model, *n* (%)			0.610

Table 1 (continued)

Parameter	LTPR (*N* = 1089)	Non-LTPR (*N* = 1950)	*P*-value
AB	107 (9.83)	203 (10.41)	
Non-AB	982 (90.17)	1747 (89.59)	

BMI, body mass index; MA(ADP), adenosine diphosphate (ADP)-induced platelet maximum amplitude; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricle ejection fraction; PLT, platelet count; MPV, mean platelet volume; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus

In the A/non-A model, after adjusting for significant variables identified in the univariate model analysis (Table 2), multivariate logistic regression reported that blood type A was independently related to LTPR (adjusted OR $_{\text{A vs. non-A}}$: 0.804, 95% CI 0.674–0.958, $P = 0.015$). In additional, HB, PLT, and ACS were also independently associated with LTPR (all $P < 0.05$) (Table 3).

In the B/non-B and AB/non-AB model, after adjusting for significant variables identified in the univariate analysis, multivariate logistic regression revealed that blood types B and AB were not related to the LTPR (all $P > 0.05$) (Table 4).

We further subdivided non-A blood types into O, B and AB. Compared with type A, only type O was independently related to LTPR (adjusted OR $_{\text{O vs. A}}$: 1.409, 95% CI 1.147–1.729, $P = 0.001$). Additionally, HB, PLT, and ACS were independently associated with LTPR (all $P < 0.05$). In comparison with blood type O, both type A and type B were independently associated with LTPR (adjusted OR $_{\text{A vs. O}}$: 0.710, 95% CI 0.578–0.872, $P = 0.001$; adjusted OR $_{\text{B vs. O}}$: 0.823, 95% CI 0.679–0.998, $P = 0.047$). HB, PLT, and ACS remained independently associated with LTPR in these comparisons (all $P < 0.05$) (Table 5).

Subgroup analysis

In the subgroup analysis, we investigated the interactions of blood type O and type A with LTPR, stratified by potential risk factors for age, sex, ACS, and hypertension.

In the O/non-O model, the association between blood type O and LTPR was not significant for age, sex, ACS, or hypertension (All P for interaction > 0.05). Similarly, in the A/non-A model, the relationship between blood type A and LTPR was not significant for age, sex, ACS, or hypertension (All P for interaction > 0.05) (Fig. 2).

In ABO blood model 1, compared with blood type A, the association between blood type O and LTPR was not significant for age, sex, ACS, or hypertension (All P for interaction > 0.05). (Fig. 3).

In conclusion, after adjusting for potential confounders, no significant interactions were found between blood type O, type A and the subgroup variables. These findings demonstrated that the effects of these blood types on LTPR are independent of the specific factors tested.

Discussion

This research utilized a large sample ($n = 3,039$), real-world, prospective cohort to examine the associations between ABO blood types and LTPR in patients with CAD and comorbid T2DM undergoing PCI with clopidogrel treatment. The main findings were as follows: (1) Blood type O was identified as an independent factor associated with higher odds of LTPR in patients with CAD and T2DM, potentially indicating an increased likelihood of bleeding; (2) Blood type A was recognized as an independent factor related to lower odds of LTPR, suggesting a reduced tendency for bleeding complications.

ABO blood types and clopidogrel-related platelet reactivity

Our study reported the association between ABO blood types and LTPR, defined by MA (ADP) on TEG, in patients with CAD and T2DM. It is plausible that ABO blood types may affect platelet reactivity in these patients, thereby affecting their susceptibility to bleeding complications. These findings provided novel perspectives into the potential mechanisms underlying platelet reactivity in this population.

Our research focused on CAD patients with comorbid T2DM undergoing PCI and demonstrated that blood type O can significantly affect platelet reactivity, potentially increasing the odds of bleeding events. Previous studies have also highlighted the importance of blood type O in bleeding across various conditions. For instance, in a group of 111 patients with left ventricular assist devices, blood type O was related to a significantly higher odds of bleeding complications within one year [14]. Dini et al. confirmed that blood type O was prevalent among patients with unknown cause bleeding and was associated with increased severity of bleeding [15]. Previous studies have reported that blood type O are at higher likelihood of bleeding complications, including severe traumatic bleeding, postpartum hemorrhage, and gastrointestinal bleeding, compared to those with non-O blood types [9, 16].

Table 2 Logistic regression for LTPR (univariate logistic regression)

Variables	Crude OR	95% CI	*P*-value
Sex	1.995	1.660–2.398	< 0.001
Age	0.988	0.980–0.995	0.001
BMI	0.992	0.969–1.015	0.493
Smoking history	1.454	1.250–1.693	< 0.001
ACS	0.778	0.670–0.902	< 0.001
Hyperlipidemia	0.930	0.788–1.099	0.395
Hypertension	0.818	0.696–0.960	0.014
COPD	1.215	0.727–2.029	0.457
Family history of CHD	1.018	0.857–1.209	0.842
Cerebrovascular disease history	0.882	0.701–1.018	0.281
Peripheral vascular disease	1.221	0.833–1.788	0.306
Prior myocardial infarction	1.244	1.040–1.487	0.017
Prior PCI	1.237	1.051–1.456	0.011
Prior CABG	1.111	0.794–1.554	0.540
LVEF	1.004	0.993–1.014	0.496
Hemoglobin	1.030	1.024–1.035	< 0.001
PLT	0.997	0.996–0.998	< 0.001
MPV	1.033	0.955–1.118	0.417
LDL-C	0.841	0.772–0.915	< 0.001
HDL-C	1.078	0.815–1.427	0.597
TC	0.874	0.815–0.937	< 0.001
Triglyceride	0.988	0.927–1.053	0.713
Glucose	0.972	0.942–1.004	0.085
Glycosylated hemoglobin	0.949	0.894–1.006	0.078
eGFR	1.005	1.000-1.010	0.043
The duration of DM	0.995	0.980–1.010	0.484
Use of hypoglycemic drugs	1.095	0.815–1.470	0.547
Use of insulin	0.870	0.713–1.061	0.169
Use of metformin	1.155	0.937–1.425	0.177
Use of alpha-glucosidase inhibitors	1.097	0.873–1.380	0.427
Use of sulfonylureas	1.251	0.957–1.635	0.102
Use of non-sulfonylurea insulin secretagogues	1.033	0.712-1.500	0.863
Use of thiazolidinediones	1.702	0.653–4.435	0.276
O /non-O model	1.277	1.087–1.499	0.003
A /non-A model	0.758	0.639–0.898	0.001
B /non-B model	1.040	0.888–1.217	0.628
AB /non-AB model	0.938	0.733-1.200	0.610
Blood model			
A			Ref
O	1.454	1.193–1.773	< 0.001
B	1.258	1.036–1.529	0.021
AB	1.157	0.878–1.525	0.300

BMI, body mass index; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricle ejection fraction; PLT, platelet count; MPV, mean platelet volume; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; OR, odd ratio; CI, confidence interval

As for blood type A, few studies have reported an association with bleeding. To our knowledge, only one study has indicated an elevated risk of thrombotic events in individuals who had blood type A [17]. The specific mechanism of the protective influence of blood type A on bleeding events could be useful for further exploration.

Previous studies also have demonstrated that sex, PLT and HB are related to platelet reactivity [13, 18–20]. Our study also indicates that these factors are related to LTPR in patients undergoing PCI. Despite our efforts to include these variables in the multivariate regression model, blood type O and blood type A remained independent indicators of LTPR. This

Table 3 Multivariate logistic regression for LTPR (O/non-O model and A/non-A model)

Variables	O/non-O model		A/non-A model	
	Adjusted OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
Sex	1.033 (0.801–1.331)	0.804	1.034 (0.802–1.332)	0.799
Age	1.000 (0.990–1.010)	0.993	1.000 (0.989–1.010)	0.943
Smoking history	1.082 (0.901-1.300)	0.399	1.096 (0.912–1.316)	0.327
ACS	0.824 (0.705–0.964)	0.015	0.817 (0.699–0.955)	0.011
Hypertension	0.880 (0.744–1.042)	0.138	0.883 (0.746–1.045)	0.149
Prior MI	1.058 (0.870–1.287)	0.570	1.058 (0.870–1.286)	0.574
Prior PCI	1.127 (0.944–1.345)	0.185	1.136 (0.952–1.355)	0.157
Hemoglobin	1.030 (1.023–1.036)	<0.001	1.029 (1.023–1.036)	<0.001
PLT	0.998 (0.997-1.000)	0.018	0.998 (0.997-1.000)	0.029
LDL-C	0.890 (0.707–1.119)	0.318	0.889 (0.707–1.119)	0.317
TC	0.932 (0.769–1.128)	0.469	0.934 (0.772–1.131)	0.486
eGFR	0.998 (0.991–1.004)	0.491	0.998 (0.991–1.004)	0.443
Non-O	Ref		--	--
O	1.298 (1.099–1.534)	**0.002**	--	--
Non-A	--	--	Ref	
A	--	--	0.804 (0.674–0.958)	**0.015**

MI, myocardial infarction; PCI, percutaneous coronary intervention; PLT, platelet count; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; eGFR, estimated glomerular filtration rate; OR, odd ratio; CI, confidence interval

Table 4 Multivariate logistic regression for LTPR (B/non-B model and AB/non-AB model)

Variables	B/non-B model		AB/non-AB model	
	Adjusted OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
Sex	1.026 (0.796–1.322)	0.842	1.031 (0.800-1.329)	0.812
Age	0.999 (0.989–1.010)	0.992	1.000 (0.989–1.010)	0.925
Smoking history	1.088 (0.906–1.306)	0.367	1.086 (0.904–1.304)	0.377
ACS	0.814 (0.697–0.952)	0.010	0.815 (0.697–0.952)	0.010
Hypertension	0.886 (0.749–1.048)	0.159	0.888 (0.750–1.050)	0.165
Prior MI	1.053 (0.866–1.279)	0.607	1.054 (0.867–1.281)	0.597
Prior PCI	1.131 (0.948–1.349)	0.171	1.129 (0.946–1.347)	0.178
Hemoglobin	1.030 (1.023–1.036)	<0.001	1.030 (1.023–1.036)	<0.001
PLT	0.998 (0.997-1.000)	0.026	0.998 (0.997-1.000)	0.026
LDL-C	0.880 (0.700-1.107)	0.276	0.882 (0.701–1.109)	0.282
TC	0.937 (0.774–1.134)	0.506	0.936 (0.774–1.133)	0.499
eGFR	0.997 (0.991–1.004)	0.431	0.998 (0.991–1.004)	0.442
B	0.981(0.833–1.155)	0.816	--	--
Non-B	Ref		--	--
AB	--	--	0.915 (0.710–1.180)	0.494
Non-AB	--	--	Ref	

MI, myocardial infarction; PCI, percutaneous coronary intervention; PLT, platelet count; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; eGFR, estimated glomerular filtration rate; OR, odd ratio; CI, confidence interval

suggests that blood type itself independently influences platelet reactivity in PCI patients.

Potential mechanisms

The exact mechanisms by which ABO blood types influence platelet reactivity to clopidogrel remain uncertain. Potential mechanisms include the expression of A and B antigens on red blood cell surfaces in individuals with blood type A and B, respectively, while individuals with blood type O lack these antigens and express only the H antigen, a precursor to A and B [21]. Among individuals possessing A and B antigens, the levels of factor VIII (FVIII) and von Willebrand factor (vWF) are notably elevated [22]. This contributes to the posttranslational glycosylation of proteins induced by A and B antigens, and the degree of glycosylation can decrease the clearance rate of vWF and FVIII. As a result, individuals with blood type O, lacking A and B antigens, tend to have lower levels of FVIII and vWF due to their faster clearance rates. VWF

Table 5 Multivariate logistic regression for LTPR (ABO blood model)

Variables	ABO blood model 1		ABO blood model 2	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex	1.039 (0.806–1.339)	0.770	0.963 (0.747–1.241)	0.770
Age	1.000 (0.990–1.010)	0.995	1.000 (0.990–1.010)	0.995
Smoking history	1.087 (0.904–1.305)	0.375	1.087 (0.904–1.305)	0.375
ACS	0.824 (0.705–0.964)	0.015	0.817 (0.699–0.955)	0.011
Hypertension	0.881 (0.744–1.042)	0.139	0.881 (0.744–1.042)	0.139
Prior MI	1.061 (0.873–1.290)	0.552	1.061 (0.873–1.290)	0.552
Prior PCI	1.129 (0.946–1.348)	0.178	1.129 (0.946–1.348)	0.178
Hemoglobin	1.029 (1.023–1.036)	<0.001	1.029 (1.023–1.036)	<0.001
PLT	0.998 (0.997-1.000)	0.021	0.998 (0.997-1.000)	0.021
LDL-C	0.894 (0.710–1.125)	0.340	0.894 (0.710–1.125)	0.340
TC	0.931 (0.768–1.127)	0.461	0.931 (0.768–1.127)	0.461
eGFR	0.998 (0.991–1.004)	0.494	0.998 (0.991–1.004)	0.494
A	Ref		0.710 (0.578–0.872)	**0.001**
O	1.409 (1.147–1.729)	**0.001**	Ref	
B	1.159 (0.947–1.418)	0.152	0.823 (0.679–0.998)	0.047
AB	1.083 (0.815–1.439)	0.580	0.769 (0.583–1.016)	0.064

ABO blood model1: non-A blood types were divided into B, AB and O

ABO blood model2: non-O blood types were divided into B, AB and A

MI, myocardial infarction; PCI, percutaneous coronary intervention; PLT, platelet count; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; eGFR, estimated glomerular filtration rate; OR, odd ratio; CI, confidence interval

binds to the GPIb-IX-V complex, triggering platelet activation [23, 24]. It also binds to FVIII, stabilizing it in circulation and preventing rapid degradation. When VWF or FVIII is absent or dysfunctional, platelet activation is impaired, increasing the risk of bleeding events [25, 26]. Therefore, in healthy people, individuals with blood type O may have lower baseline platelet activity due to lower levels of vWF/FVIII, whereas individuals with blood type A, due to higher levels of VWF/FVIII, may have greater baseline platelet activity. Notably, reduced levels of FVIII and vWF are related to an elevated risk of bleeding [10, 11]. Therefore, compared to individuals with blood type A, blood type O are believed to have a higher risk for bleeding events [10, 22].

A U.S. study involving 8,582 patients undergoing PCI found that those with T2DM exhibited higher platelet reactivity [27]. Recent studies have shown that inflammation may increase platelet reactivity [7, 28]. T2DM is characterized by endothelial dysfunction and chronic inflammation, both of which contribute to platelet activation. Therefore, we hypothesize that elevated inflammation in T2DM patients may increase platelet reactivity [29, 30]. Additionally, the A allele has been linked to increased vascular inflammation, promoting the release of inflammatory factors that accelerate atherosclerosis [31, 32]. Based on this, we speculate that individuals with blood type A may have higher platelet reactivity than those with blood type O, potentially reducing bleeding risk. Further studies are needed to clarify the mechanisms linking ABO blood types and platelet reactivity in T2DM patients.

Clinical implications and future directions

The current research is the first to explore the link between the ABO blood types and LTPR, utilizing the MA (ADP) of the TEG as an indicator. Our study revealed that in patients who received clopidogrel, blood type O was independently related to higher odds of LTPR, indicating a greater likelihood of bleeding, while blood type A was independently related to lower odds of LTPR, suggesting a reduced likelihood of bleeding, which may partially elucidate new insights and mechanisms.

Blood type is a universal attribute in individuals, and our study suggests that, in patients with CAD and T2DM, the influence of blood type on platelet reactivity may have been previously underestimated. In the future, the noteworthy findings of this study underscore the importance of physicians being mindful of the blood type of CAD and comorbid T2DM patients upon admission. This heightened awareness can facilitate diligent monitoring of bleeding tendencies in clinical settings.

Limitation

There are several limitations to the analysis in our study. Firstly, our study was a single-center study that may limit the generalizability of our results. Secondly, we did not record the dose and duration of clopidogrel,

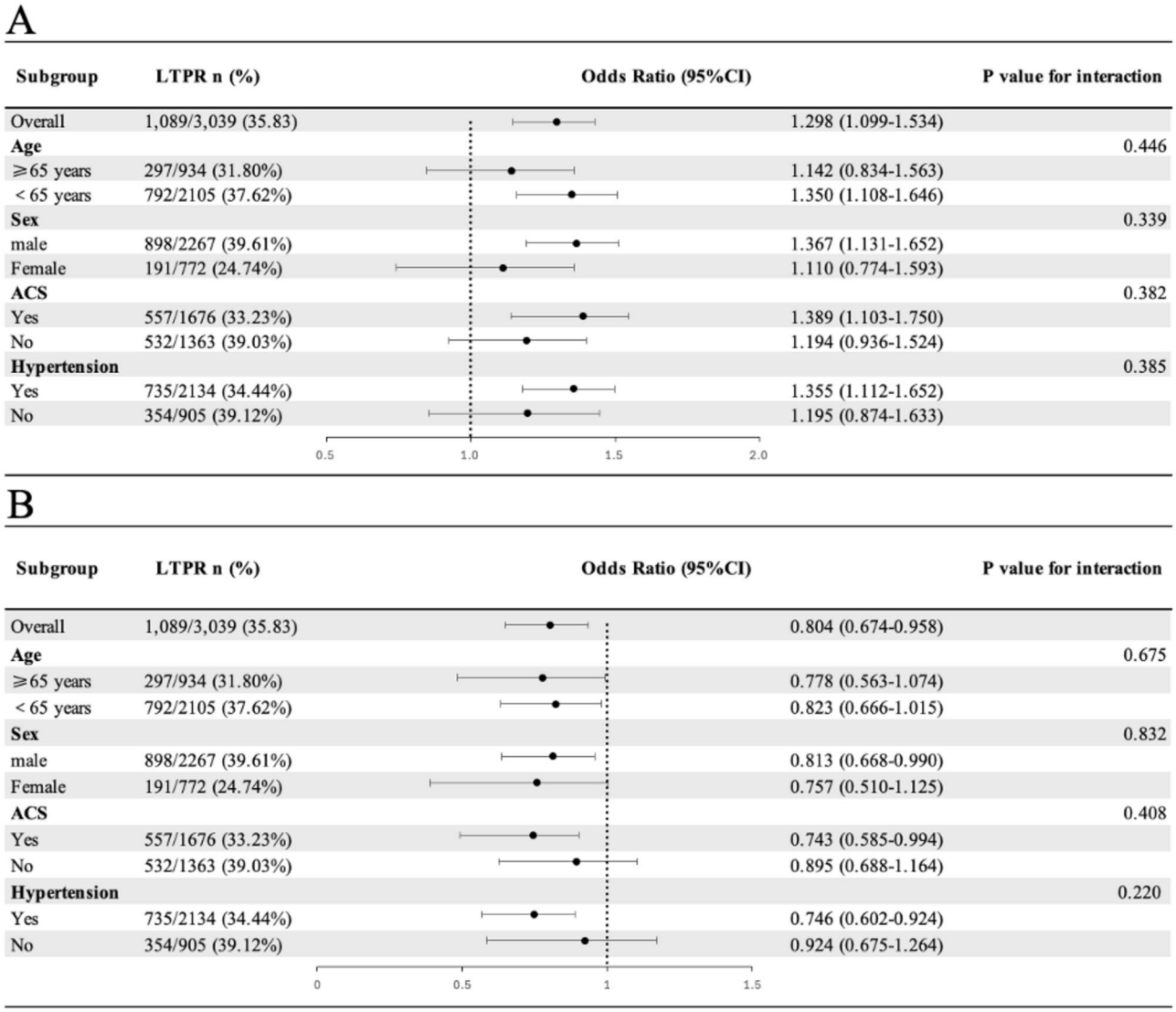

Fig. 2 Subgroup analysis of the association of O/non-O model and A/non-A model with LTPR
A: O/non-O blood model; B: A/non-A blood model
ACS, acute coronary syndrome; LTPR, low on-treatment platelet reactivity

which are important factors that can influence platelet reactivity in PCI patients [33]. Third, despite our efforts to control multiple variables, this study was inevitably subject to several confounding factors. Fourth, we focused only on the ABO blood types in the Chinese population. As the distribution of blood types varies worldwide, further research should explore the RhD system and include diverse ethnic populations to gain a more comprehensive understanding [17]. Fifth, this study lacked detailed procedural records regarding the platelet reactivity test, such as tube type, time from venipuncture to testing, and needle gauge. Finally, although this study observed the impact of T2DM on the relationship between ABO blood types and LTPR, this finding was an exploratory analysis. Future studies are needed to further validate this finding in the future.

Conclusions

This large-sample research explored the relationship between ABO blood types and LTPR in CAD patients with T2DM receiving PCI and treated with clopidogrel. Blood type O was identified as an independent factor associated with increased odds of LTPR, while blood type A served as an independent protective factor. These findings provide a novel perspective on the importance of ABO blood types in CAD patients with comorbid T2DM, though further investigation into the underlying mechanisms is needed.

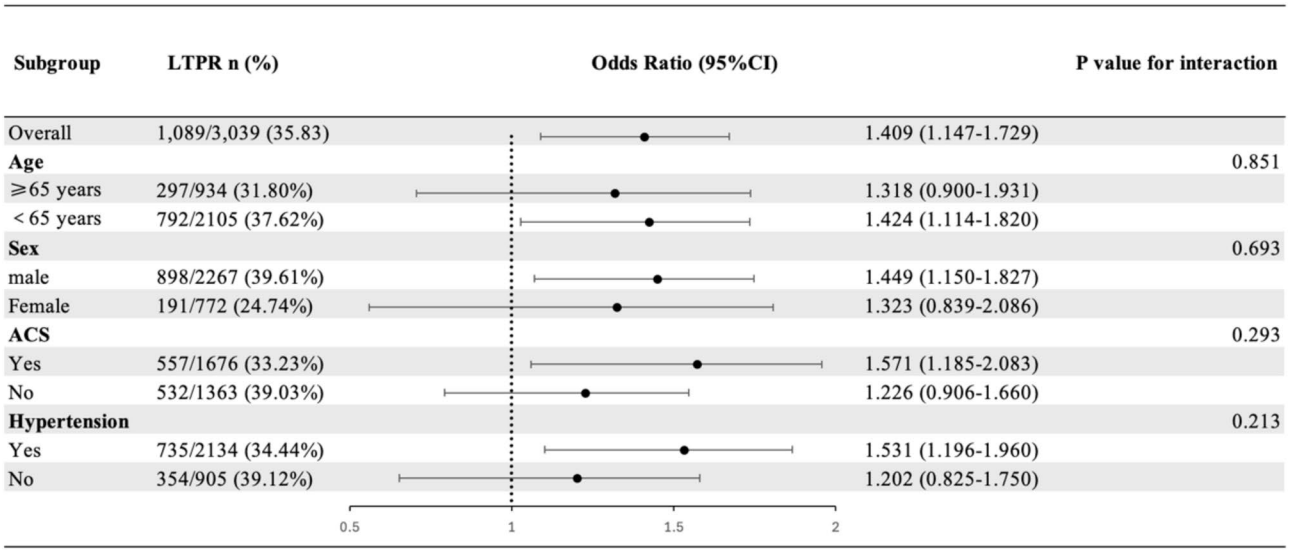

Fig. 3 Subgroup analysis of the association of blood type O with LTPR in blood model 1
ABO blood model 1: non-A blood types were divided into B, AB and O
ACS, acute coronary syndrome; LTPR, low on-treatment platelet reactivity

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
eGFR	Estimated glomerular filtration rate
FVIII	Factor VIII
HB	Hemoglobin
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LTPR	Low on-treatment platelet reactivity
LVEF	Left ventricle ejection fraction
MA(ADP)	Adenosine diphosphate-induced platelet maximum amplitude
MPV	Mean platelet volume
OR	Odd ratio
PCI	Percutaneous coronary intervention
PLT	Platelet count
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TEG	Thromboelastogram
vWF	von Willebrand factor

Supplementary Information

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Supplementary Material 1

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Author contributions
ML designed this study, analyzed data, and drafted the manuscript. JL, KY, KZ, PZ, XT, and DY contributed to the acquisition, analysis, or interpretation of data. XZ, JY, YY, and RG developed the idea and revised the manuscript. All authors reviewed the manuscript.

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Data availability
Due to ethical restrictions imposed by the informed consent agreements established at study commencement, the research datasets are subject to controlled access protocols. Interested researchers may submit formal data requests to the corresponding author. Such requests will require subsequent approval by the Institutional Review Board of the State Key Laboratory of Cardiovascular Disease at Fu Wai Hospital, National Center for Cardiovascular Diseases.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the Fuwai hospital institutional review board (approval number: 2013 – 449). The patients/participants provided written informed consent to participate in this study.

Consent for publication
All the authors have approved the manuscript that is enclosed for publication.

Competing interests
The authors declare no competing interests.

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