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Article

Residual Platelet Reactivity and Dyslipidemia in Post-CABG Patients Undergoing Repeat Revascularization: Insights from Kazakhstan

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Abstract

Background: Coronary artery bypass grafting (CABG) is a standard treatment for advanced coronary artery disease (CAD). Despite its effectiveness, many patients develop recurrent ischemia requiring repeat revascularization. Residual platelet reactivity (RPR) and dyslipidemia are considered important contributors to graft failure and disease progression. This study investigated the association of RPR and dyslipidemia with repeat revascularization in post-CABG patients. **Methods:** A observational cohort study was performed at a tertiary cardiology center in Kazakhstan. A total of 200 patients with prior CABG who underwent repeat coronary angiography between 2023 and 2024 for recurrent ischemic symptoms were included. Clinical data, comorbidities, lipid profiles, and antiplatelet response were analyzed. RPR was measured with the VerifyNow P2Y12 assay where available. Dyslipidemia was defined according to current European guidelines, 2019/2021. **Results:** Elevated RPR was found in 45% (n = 90) of patients despite dual antiplatelet therapy. Poor lipid control, especially increased low-density lipoprotein cholesterol (LDL-C) and total cholesterol was common among patients undergoing repeat percutaneous coronary intervention (PCI). Both RPR and dyslipidemia were independently associated with native coronary disease progression and graft failure. **Conclusions:** RPR and dyslipidemia are frequent and clinically relevant predictors of repeat revascularization after CABG. Optimizing antiplatelet and lipid-lowering therapy should be a priority in secondary prevention for this high-risk group. These results are particularly important in the Central Asian setting, where post-CABG management strategies require further improvement.

Keywords: coronary artery bypass grafting; residual platelet reactivity; dyslipidemia; repeat revascularization; dual antiplatelet therapy; Kazakhstan

1. Introduction

Coronary artery bypass grafting (CABG) remains a cornerstone in the management of advanced coronary artery disease (CAD), especially in patients with multivessel involvement. While surgical revascularization provides symptomatic relief and mortality benefit, a considerable proportion of patients continue to experience recurrent ischemic symptoms and adverse cardiovascular events during follow-up.

Platelets play a central role in the pathogenesis of atherosclerosis and arterial thrombosis. High residual platelet reactivity (HRPR), even under antiplatelet therapy, is a well-established predictor of major adverse cardiovascular events, including myocardial infarction (MI), stroke, and stent thrombosis [1,2]. Patients with multivessel CAD undergoing CABG have been shown to exhibit

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higher levels of HRPR compared to those with single-vessel disease. Several comorbidities—including dyslipidemia, anemia, chronic kidney disease (CKD), reduced left ventricular ejection fraction (LVEF), and overweight/obesity—are strongly associated both with HRPR and with the presence of extensive coronary disease, thereby amplifying the risk of recurrent ischemic events [3,4].

The prothrombotic role of platelets is particularly important in patients receiving long-term antiplatelet therapy aimed at reducing MI and stroke incidence. Anemia, common among patients with chronic heart failure (CHF), is linked to impaired response to clopidogrel, increased HRPR, higher hospitalization rates, and worse survival [5–7]. Renal dysfunction further diminishes antiplatelet efficacy and contributes to poor outcomes [8]. HRPR has consistently been recognized as a poor prognostic marker in acute coronary syndrome (ACS) [9]. Smoking, dyslipidemia, and elevated cholesterol levels additionally enhance platelet activation and thrombotic risk [4,5]. Moreover, obesity—particularly class I—has been associated with increased HRPR during antiplatelet therapy [10].

In the post-CABG setting, hemostatic alterations induced by cardiopulmonary bypass may further influence platelet function and predispose to enhanced platelet activation [11]. The pathophysiological mechanism linking HRPR to cardiovascular complications primarily involves exaggerated platelet aggregation and thrombus formation [12–14]. Consequently, HRPR is considered an independent risk factor for recurrent ischemic events, including MI, graft failure, stent thrombosis, and cardiovascular death [15,16].

Importantly, dyslipidemia represents a modifiable determinant of both platelet hyperreactivity and atherosclerotic progression. Failure to achieve guideline-recommended low-density lipoprotein cholesterol (LDL-C) targets—particularly <1.4 mmol/L in very-high-risk patients according to the 2019/2021 ESC guidelines—significantly increases the risk of recurrent ischemia and need for repeat revascularization. Thus, strict lipid control remains a cornerstone of secondary prevention in post-CABG patients and is crucial for improving long-term outcomes.

In this study, we analyzed 200 post-CABG patients from a tertiary cardiac center in Kazakhstan. Recurrent angina was observed in 94% (n=188), and 68% (n=136) required repeat percutaneous coronary intervention (PCI) after coronary angiography. Our aim was to identify the predominant clinical phenotypes associated with these outcomes, with particular emphasis on dyslipidemia and inadequate LDL-C control, residual platelet reactivity despite dual antiplatelet therapy, anemia, CKD, and heart failure (HF).

2. Materials and Methods

Study Design and Setting

This observational single-center cohort study was conducted from January 2023 to December 2024 at the Research Institute of Cardiology and Internal Medicine, a tertiary-level cardiovascular center in Almaty, Kazakhstan. The study aimed to evaluate residual platelet reactivity and dyslipidemia as risk factors for repeat revascularization in patients with established coronary artery disease (CAD) who previously underwent coronary artery bypass grafting (CABG).

Patient Population

Eligible participants were adult patients (≥18 years) with a documented history of coronary artery bypass grafting (CABG) and a diagnosis of stable coronary artery disease (CAD) who were admitted for repeat coronary angiography due to recurrent ischemic symptoms.

Inclusion Criteria:

Prior history of CABG
Documented stable CAD

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Clinical and/or instrumental evidence of recurrent myocardial ischemia (e.g., angina, positive stress test, ischemic ECG changes)

Exclusion Criteria:

Presence of atrial fibrillation

Current use of oral anticoagulant therapy (e.g., rivaroxaban, apixaban, dabigatran)

Diagnosis of acute coronary syndrome (ACS) at the time of admission

A detailed flowchart of patient selection, including inclusion and exclusion criteria, is presented in **Figure 1**.

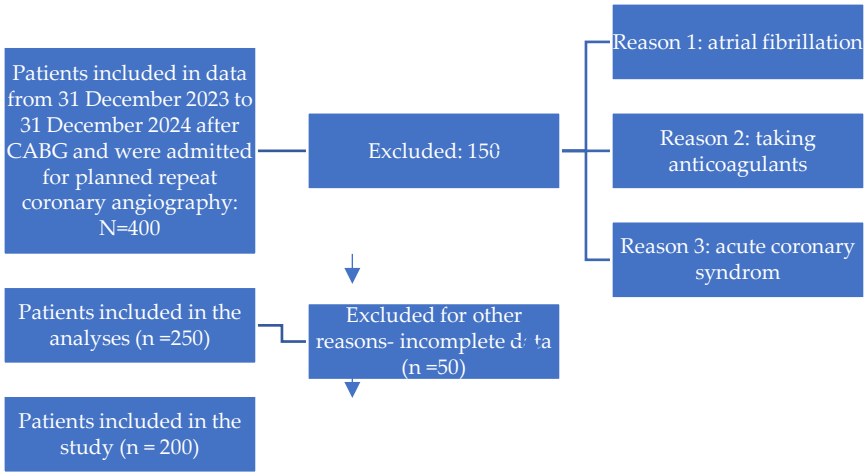

Figure 1. The flow chart of patients.

Residual Platelet Reactivity Assessment

Residual platelet reactivity (RPR) was evaluated using the VerifyNow P2Y12 assay (Instrumentation Laboratory, Bedford, MA, USA), a point-of-care system that quantifies platelet inhibition and reports results as P2Y12 Reaction Units (PRU). High residual platelet reactivity (HRPR) was defined as PRU ≥208, in accordance with current international consensus guidelines.

Clinical and Laboratory Data Collection

Baseline demographic, clinical, and pharmacological characteristics were extracted from electronic medical records. The following parameters were systematically evaluated:

Lipid profile: Total cholesterol, LDL-C, HDL-C, triglycerides

Renal function: Serum creatinine and estimated glomerular filtration rate (eGFR) to identify chronic kidney disease (CKD)

Hemoglobin level: Assessed for anemia according to WHO criteria

Left ventricular ejection fraction (LVEF): Measured via transthoracic echocardiography

Body mass index (BMI): Used to classify overweight and obesity

Cardiovascular complications: Including heart failure, diabetes mellitus, and prior myocardial infarction

All patients were treated with guideline-directed medical therapy in accordance with the 2024 European Society of Cardiology (ESC) recommendations for the management of chronic coronary syndromes.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee of Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan (Protocol No. 11(134); Date: 04 November 2022). Written informed consent was obtained from all participants prior to enrollment.

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Statistical Analysis

The data are presented as Median [Quartile 1; Quartile 3], as the majority of the quantitative variables do not follow a normal distribution. Between-group comparisons were performed using the Mann–Whitney U test for quantitative variables, or the chi-squared test (Fisher's exact test when the number of observations was small) for qualitative variables. Categorical variables were expressed as **frequencies and percentages.** Normality of continuous variables, including PRU values, was assessed using the Shapiro–Wilk test**.** For comparisons of continuous variables between groups (e.g., HRPR vs. non-HRPR) **Mann–Whitney U test** was used as appropriate. Categorical variables were analyzed using the **Chi-square test** or **Fisher's exact test.** A stepwise logistic regression analysis was performed to identify predictors associated with the risk of stenting after coronary artery bypass grafting (CABG). A **p-value < 0.05** was considered statistically significant. All statistical tests were two-sided, and **95% confidence intervals (CIs)** were reported when relevant.

3. Results

A total of 195 post-CABG patients were included in the final analysis. Among them, 136 patients (69.7%) underwent repeat percutaneous coronary intervention (PCI), whereas 59 patients (30.3%) did not require reintervention. Baseline demographic, clinical, laboratory, and instrumental characteristics were systematically compared between the two groups (Table 1).

Table 1. Descriptive statistics of the group without re-stenting and with re-stenting.

	Without re-stenting ***N=59***	**With re-stenting** ***N=136***	**p-value**	**N**
Age	66.0 [61.5;73.0]	71.0 [65.8;75.0]	0.016	195
Gender:			0.431	195
female	13 (22.0%)	39 (28.7%)		
male	46 (78.0%)	97 (71.3%)		
Smoking:			0.001	195
No	27 (45.8%)	97 (71.3%)		
Yes	32 (54.2%)	39 (28.7%)		
Alcohol:			0.164	195
No	56 (94.9%)	134 (98.5%)		
Yes	3 (5.08%)	2 (1.47%)		
Weight	79.0 [70.0;86.5]	78.5 [70.0;85.8]	0.903	195
Height	170 [164;174]	168 [162;173]	0.438	195
BMI	27.3 [24.9;29.4]	27.6 [25.0;30.2]	0.411	195
Heredity:			0.874	195
No	37 (62.7%)	82 (60.3%)		
Yes	22 (37.3%)	54 (39.7%)		
Dyspnea:			0.776	194
No	5 (8.47%)	10 (7.41%)		
Yes	54 (91.5%)	125 (92.6%)		
Edema:			0.190	195
No	55 (93.2%)	116 (85.3%)		
Yes	4 (6.78%)	20 (14.7%)		
Pain:			0.726	195
No	2 (3.39%)	7 (5.15%)		
Yes	57 (96.6%) ?	129 (94.9%)		
Weakness:			0.104	195
No	0 (0.00%)	7 (5.15%)		

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	Without re-stenting *N=59*	With re-stenting *N=136*	p-value	N
Yes	59 (100%)	129 (94.9%)		
Heartbeat:			0.451	195
No	53 (89.8%)	115 (84.6%)		
Yes	6 (10.2%)	21 (15.4%)		
Short of breath:			0.961	195
No	43 (72.9%)	97 (71.3%)		
Yes	16 (27.1%)	39 (28.7%)		
SBP	120 [110;130]	130 [120;140]	0.041	195
DBP	80.0 [70.0;80.0]	80.0 [70.0;80.0]	0.201	195
History of myocardial infarction:			0.145	195
No	33 (55.9%)	59 (43.4%)		
Yes	26 (44.1%)	77 (56.6%)		
AH:			0.133	195
No	5 (8.47%)	4 (2.94%)		
Yes	54 (91.5%)	132 (97.1%)		
DM type 2:			0.603	195
No	42 (71.2%)	90 (66.2%)		
Yes	17 (28.8%)	46 (33.8%)		
History of Stroke:			0.400	195
No	56 (94.9%)	123 (90.4%)		
Yes	3 (5.08%)	13 (9.56%)		
CKD:			0.068	195
No	39 (66.1%)	69 (50.7%)		
Yes	20 (33.9%)	67 (49.3%)		
Stenting:			0.712	195
No	47 (79.7%)	113 (83.1%)		
Yes	12 (20.3%)	23 (16.9%)		
CABG:			0.003	195
No	10 (16.9%)	5 (3.68%)		
Yes	49 (83.1%)	131 (96.3%)		
IHD, duration	3.00 [1.00;6.50]	2.50 [1.00;10.0]	0.364	195
Hemoglobin	142 [132;154]	145 [135;155]	0.542	195
CRP	2.00 [1.24;3.56]	2.45 [1.03;4.22]	0.487	195
Glucose	5.54 [5.12;6.30]	5.80 [5.16;6.93]	0.293	195
HbA1c	6.01 [5.30;6.70]	6.05 [5.40;7.33]	0.403	195
Creatinine	80.4 [70.6;90.2]	79.0 [70.8;92.2]	0.952	195
GFR	88.0 [75.8;96.0]	81.0 [69.8;94.2]	0.279	195
Potassium	4.40 [4.20;4.60]	4.30 [4.10;4.60]	0.590	195
Sodium	142 [140;144]	142 [141;144]	0.268	195
ALT	19.0 [14.1;28.5]	18.1 [12.9;25.7]	0.453	195
AST	17.3 [13.8;25.9]	17.9 [14.9;23.1]	0.977	195
TC	4.24 [3.41;5.25]	4.50 [3.70;5.22]	0.419	195
LDL	2.58 [2.00;3.17]	2.42 [2.00;3.20]	0.569	195
HDL	1.00 [0.99;1.00]	1.00 [0.96;1.03]	0.809	195
TG	1.50 [1.00;1.98]	1.29 [1.00;1.75]	0.083	195
Troponin I	20.0 [13.4;95.4]	14.3 [10.3;32.8]	0.002	195
TSH	2.00 [1.47;2.90]	2.00 [1.39;3.15]	0.773	195
Thyroxine	14.1 [12.0;16.0]	14.0 [11.6;16.2]	0.945	193
PTI	94.9 [80.3;103]	95.8 [77.5;105]	0.627	195
INR	1.07 [1.04;1.17]	1.04 [0.99;1.14]	0.039	195

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	Without re-stenting *N=59*	With re-stenting *N=136*	p-value	N
APTT	31.1 [28.8;36.5]	31.6 [28.7;35.7]	0.737	195
EDV	162 [129;206]	136 [113;179]	0.038	195
ESV	80.0 [45.5;116]	61.5 [45.8;95.2]	0.222	195
SV	78.0 [69.5;87.5]	77.5 [59.8;92.2]	0.466	195
sPAP	32.0 [23.0;44.0]	35.0 [24.5;42.0]	0.917	194
EF	47.0 [41.5;59.0]	52.0 [44.0;59.2]	0.235	195
LA	3.80 [3.60;4.55]	3.90 [3.50;4.40]	0.638	195
EDD	5.70 [5.20;6.30]	5.30 [4.97;6.00]	0.081	195
ESD	4.20 [3.35;4.90]	3.80 [3.30;4.60]	0.240	195
LVPW	1.05 [0.90;1.20]	1.10 [1.00;1.20]	0.030	195
IVS	1.10 [0.95;1.27]	1.10 [1.00;1.30]	0.924	195
MV:			0.858	195
No	4 (6.78%)	13 (9.56%)		
1 degree.	36 (61.0%)	75 (55.1%)		
2 degree.	13 (22.0%)	36 (26.5%)		
3 degree.	6 (10.2%)	11 (8.09%)		
4 degree.	0 (0.00%)	1 (0.74%)		
TV:			0.437	195
No	9 (15.3%)	22 (16.2%)		
1 degree.	32 (54.2%)	67 (49.3%)		
2 degree.	16 (27.1%)	46 (33.8%)		
3 degree.	2 (3.39%)	1 (0.74%)		
AV:			0.309	195
No	30 (50.8%)	71 (52.2%)		
1 degree.	22 (37.3%)	49 (36.0%)		
2 degree.	5 (8.47%)	15 (11.0%)		
3 degree.	0 (0.00%)	1 (0.74%)		
Stenosis	2 (3.39%)	0 (0.00%)		
RV	3.00 [2.80;3.40]	3.10 [2.90;3.40]	0.566	195
LV aneurysm:			0.990	195
No	50 (84.7%)	117 (86.0%)		
Yes	9 (15.3%)	19 (14.0%)		
Heart Rate	75.0 [66.0;82.0]	71.5 [65.0;83.2]	0.496	195
USD of BCA:			1.000	195
No	24 (40.7%)	56 (41.2%)		
Yes	35 (59.3%)	80 (58.8%)		
RCA, degree:			0.117	195
minor	44 (74.6%)	84 (61.8%)		
significant	15 (25.4%)	52 (38.2%)		
LAD, degree:			0.002	195
Minor	43 (72.9%)	64 (47.1%)		
Significant	16 (27.1%)	72 (52.9%)		
LCA, degree:			0.235	195
Minor	55 (93.2%)	117 (86.0%)		
Significant	4 (6.78%)	19 (14.0%)		
CA, degree:			0.002	195
Minor	51 (86.4%)	85 (62.5%)		
significant	8 (13.6%)	51 (37.5%)		
DB, degree:			0.001	195
Minor	54 (91.5%)	94 (69.1%)		

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	Without re-stenting *N=59*	With re-stenting *N=136*	p-value	N
significant	5 (8.47%)	42 (30.9%)		
PIVB, degree:			0.006	195
Minor	58 (98.3%)	113 (83.1%)		
Significant	1 (1.69%)	23 (16.9%)		
IA, degree:			0.369	195
Minor	56 (94.9%)	133 (97.8%)		
significant	3 (5.08%)	3 (2.21%)		
OMB, degree:			0.002	195
Minor	56 (94.9%)	102 (75.0%)		
Significant	3 (5.08%)	34 (25.0%)		
Number of shunts	2.00 [2.00;3.00]	3.00 [2.00;3.00]	<0.001	195
Number of affected vessels	3.00 [2.00;3.00]	4.00 [3.75;5.00]	<0.001	195
Statins: Yes	59 (100%)	136 (100%)	.	195
Ezetimibe:			<0.001	195
No	59 (100%)	89 (65.4%)		
Yes	0 (0.00%)	47 (34.6%)		
Angina after CABG:			<0.001	195
No	7 (11.9%)	0 (0.00%)		
Yes	52 (88.1%)	136 (100%)		
Mortality after CABG:			1.000	195
No	58 (98.3%)	132 (97.1%)		
Yes	1 (1.69%)	4 (2.94%)		
Stenting after CABG:			<0.001	195
No	59 (100%)	0 (0.00%)		
Yes	0 (0.00%)	136 (100%)		
PRU	145 [140;155]	230 [200;274]	<0.001	195
Dyslipidemia:			1.000	195
No	2 (3.39%)	4 (2.94%)		
Yes	57 (96.6%)	132 (97.1%)		
Anemia:			0.941	195
No	52 (88.1%)	122 (89.7%)		
Yes	7 (11.9%)	14 (10.3%)		
CKD:			0.977	195
No	53 (89.8%)	124 (91.2%)		
Yes	6 (10.2%)	12 (8.82%)		
Obesity:			0.406	195
No	17 (28.8%)	30 (22.1%)		
Yes	42 (71.2%)	106 (77.9%)		
RPR:			<0.001	195
Therapeutic window	59 (100%)	46 (33.8%)		
HRPR	0 (0.00%)	90 (66.2%)		

Demographic and Clinical Characteristics

Patients requiring repeat PCI were significantly older than those without reintervention (median age: 71.0 [IQR 65.8–75.0] vs. 66.0 [61.5–73.0] years; p = 0.016). No significant difference in sex distribution was observed (p = 0.431). Current smoking was more frequent in the non-reintervention group (54.2% vs. 28.7%; p = 0.001), whereas alcohol consumption rates were low and comparable (p = 0.164). Systolic blood pressure was higher in the repeat PCI group (130 [120–140] vs. 120 [110–130] mmHg; p = 0.041), while diastolic pressure did not differ significantly.

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Comorbidities and Medical History

The prevalence of hypertension, diabetes mellitus, prior myocardial infarction, stroke, chronic kidney disease (CKD), anemia, and obesity was similar between groups. However, a higher frequency of prior CABG was noted among patients undergoing reintervention (96.3% vs. 83.1%; p = 0.003).

Biochemical and Hematological Parameters

No significant group differences were found in lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides), glycemic control (glucose, HbA1c), renal function (creatinine, eGFR), liver enzymes (ALT, AST), inflammatory markers (CRP), or thyroid function (TSH, T4). Interestingly, cardiac troponin levels were lower in the reintervention group (14.3 [10.3–32.8] vs. 20.0 [13.4–95.4] ng/L; $\boldsymbol{p}$ = 0.002), possibly reflecting differences in post-CABG myocardial injury dynamics.

Platelet Reactivity

Patients undergoing repeat PCI exhibited significantly higher platelet reactivity. Median PRU was 230 [200–274] versus 145 [140–155] ($\boldsymbol{p}$ < 0.001). Moreover, high residual platelet reactivity (HRPR) was present in 66.2% of the reintervention group compared to 0% in the control group ($\boldsymbol{p}$ < 0.001).

Echocardiographic Findings

End-diastolic volume (EDV) was lower in the reintervention group (136 [113–179] vs. 162 [129–206] mL; p = 0.038). Posterior wall thickness (PWT) was also higher (1.10 [1.00–1.20] vs. 1.05 [0.90–1.20] cm; p = 0.030). No significant differences were observed for LVEF, stroke volume, left atrial/ventricular dimensions, or pulmonary artery pressure.

Coronary Angiographic Findings

Patients with repeat PCI demonstrated more extensive coronary artery disease. Significant stenosis was more frequently detected in:

LAD: 52.9% vs. 27.1% (p = 0.002)

LCx: 37.5% vs. 13.6% (p = 0.002)

Diagonal branch: 30.9% vs. 8.5% (p = 0.001)

PDA: 16.9% vs. 1.7% (p = 0.006)

SVGs: 25.0% vs. 5.1% (p = 0.002)

The number of bypass grafts (3.00 [2.00–3.00] vs. 2.00 [2.00–3.00]; p < 0.001) and diseased vessels (4.00 [3.75–5.00] vs. 3.00 [2.00–3.00]; p < 0.001) was also higher in the reintervention group.

Medical Therapy

All patients received statin therapy. Ezetimibe was prescribed more frequently in the reintervention group (34.6% vs. 0%; p < 0.001), suggesting intensified lipid-lowering strategies in patients with progressive disease.

Symptoms and Outcomes

Persistent angina post-CABG was reported in all reintervention patients compared to 88.1% in the control group (p < 0.001). No significant difference in post-CABG mortality was observed.

Summary of Key Findings

High residual platelet reactivity was strongly associated with repeat revascularization.

Older age, greater coronary involvement, and higher number of bypass grafts predicted the need for reintervention.

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Despite similar baseline lipid levels, patients requiring repeat PCI were more frequently prescribed ezetimibe.

The prevalence of anemia, CKD, and diabetes was similar between groups, suggesting HRPR and coronary disease burden play a more central role in post-CABG ischemic recurrence.

Table 2. Descriptive statistics of the Therapeutic window/HRPR group.

	Therapeutic window	HRPR	p-value	N
	N=105	*N=90*		
Age	69.0 [62.0;74.0]	70.5 [65.2;75.0]	0.147	195
Gender:			0.871	195
female	29 (27.6%)	23 (25.6%)		
male	76 (72.4%)	67 (74.4%)		
Smoking:			0.030	195
No	59 (56.2%)	65 (72.2%)		
Yes	46 (43.8%)	25 (27.8%)		
Alcohol:			1.000	195
No	102 (97.1%)	88 (97.8%)		
Yes	3 (2.86%)	2 (2.22%)		
Weight	78.0 [69.0;85.0]	80.0 [70.2;88.0]	0.199	195
Height	168 [163;174]	170 [162;173]	0.838	195
BMI	27.2 [25.0;29.4]	28.1 [25.9;30.6]	0.096	195
Heredity:			0.475	195
No	67 (63.8%)	52 (57.8%)		
Yes	38 (36.2%)	38 (42.2%)		
Dyspnea:			0.739	194
No	7 (6.67%)	8 (8.99%)		
Yes	98 (93.3%)	81 (91.0%)		
Edema:			0.801	195
No	91 (86.7%)	80 (88.9%)		
Yes	14 (13.3%)	10 (11.1%)		
Pain:			0.510	195
No	6 (5.71%)	3 (3.33%)		
Yes	99 (94.3%)	87 (96.7%)		
Weakness:			0.252	195
No	2 (1.90%)	5 (5.56%)		
Yes	103 (98.1%)	85 (94.4%)		
Heartbeat:			1.000	195
No	90 (85.7%)	78 (86.7%)		
Yes	15 (14.3%)	12 (13.3%)		
Short of breath:			0.778	195
No	74 (70.5%)	66 (73.3%)		
Yes	31 (29.5%)	24 (26.7%)		
SBP	120 [115;130]	130 [120;140]	0.031	195
DBP	80.0 [70.0;80.0]	80.0 [70.0;80.0]	0.320	195
History of myocardial infarction:			0.394	195
No	53 (50.5%)	39 (43.3%)		
Yes	52 (49.5%)	51 (56.7%)		
AH:			0.510	195
No	6 (5.71%)	3 (3.33%)		
Yes	99 (94.3%)	87 (96.7%)		
DM type 2:			0.293	195
No	75 (71.4%)	57 (63.3%)		

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	Therapeutic window	HRPR	p-value	N
	N=105	*N=90*		
Yes	30 (28.6%)	33 (36.7%)		
History of Stroke:			0.031	195
No	101 (96.2%)	78 (86.7%)		
Yes	4 (3.81%)	12 (13.3%)		
CKD:			0.697	195
No	60 (57.1%)	48 (53.3%)		
Yes	45 (42.9%)	42 (46.7%)		
Stenting:			0.897	195
No	87 (82.9%)	73 (81.1%)		
Yes	18 (17.1%)	17 (18.9%)		
CABG:			0.065	195
No	12 (11.4%)	3 (3.33%)		
Yes	93 (88.6%)	87 (96.7%)		
IHD, duration	2.00 [1.00;8.00]	3.00 [1.00;9.75]	0.888	195
Hemoglobin	142 [132;154]	150 [136;156]	0.053	195
CRP	2.36 [1.27;4.10]	2.29 [1.02;4.13]	0.853	195
Glucose	5.54 [5.00;6.20]	5.90 [5.23;7.10]	0.022	195
HbA1c	6.01 [5.38;6.70]	6.06 [5.52;7.83]	0.282	195
Creatinine	80.0 [71.0;91.8]	79.0 [70.3;92.7]	0.890	195
GFR	87.0 [74.0;96.0]	81.0 [70.0;92.5]	0.361	195
Potassium	4.30 [4.10;4.50]	4.35 [4.10;4.60]	0.267	195
Sodium	142 [141;144]	142 [140;144]	0.931	195
ALT	18.0 [12.0;27.5]	19.0 [14.0;26.4]	0.473	195
AST	17.6 [13.8;25.8]	17.7 [15.0;22.7]	0.934	195
TC	4.30 [3.67;5.27]	4.50 [3.63;5.20]	0.571	195
LDL	2.43 [2.00;3.10]	2.64 [2.00;3.39]	0.546	195
HDL	1.00 [0.98;1.01]	1.00 [0.96;1.04]	0.684	195
TG	1.37 [1.00;1.80]	1.38 [1.00;1.79]	0.981	195
Troponin I	15.0 [11.0;58.7]	15.0 [11.0;40.0]	0.635	195
TSH	2.00 [1.60;3.00]	1.96 [1.25;3.18]	0.517	195
Thyroxine	13.9 [11.5;16.2]	14.7 [12.3;16.3]	0.335	193
PTI	94.5 [80.0;103]	96.3 [78.5;106]	0.209	195
INR	1.06 [1.01;1.16]	1.04 [1.00;1.15]	0.189	195
APTT	31.4 [29.0;35.9]	31.4 [28.6;36.0]	0.524	195
EDV	157 [119;194]	131 [113;174]	0.053	195
ESV	72.0 [44.0;108]	60.0 [46.0;91.2]	0.256	195
SV	78.0 [65.0;91.0]	77.0 [59.0;90.0]	0.268	195
sPAP	34.0 [23.8;44.0]	35.0 [20.8;40.8]	0.624	194
EF	49.0 [41.0;60.0]	51.7 [45.0;58.9]	0.459	195
LA	3.80 [3.50;4.40]	3.80 [3.60;4.40]	0.907	195
EDD	5.60 [5.10;6.20]	5.20 [4.90;5.90]	0.043	195
ESD	4.00 [3.30;4.80]	3.74 [3.40;4.38]	0.394	195
LVPW	1.10 [0.90;1.20]	1.10 [1.00;1.20]	0.087	195
IVS	1.10 [1.00;1.30]	1.10 [0.90;1.30]	0.366	195
MV:			0.291	195
No	7 (6.67%)	10 (11.1%)		
1 degree.	62 (59.0%)	49 (54.4%)		
2 degree.	24 (22.9%)	25 (27.8%)		
3 degree.	12 (11.4%)	5 (5.56%)		
4 degree.	0 (0.00%)	1 (1.11%)		
TV:			0.717	195

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	Therapeutic window	HRPR	p-value	N
	N=105	*N=90*		
No	14 (13.3%)	17 (18.9%)		
1 degree.	55 (52.4%)	44 (48.9%)		
2 degree.	34 (32.4%)	28 (31.1%)		
3 degree.	2 (1.90%)	1 (1.11%)		
AV:			0.070	195
No	51 (48.6%)	50 (55.6%)		
1 degree.	44 (41.9%)	27 (30.0%)		
2 degree.	7 (6.67%)	13 (14.4%)		
3 degree.	1 (0.95%)	0 (0.00%)		
Stenosis	2 (1.90%)	0 (0.00%)		
RV	3.00 [2.90;3.40]	3.10 [2.90;3.30]	0.893	195
LV aneurysm:			0.862	195
No	89 (84.8%)	78 (86.7%)		
Yes	16 (15.2%)	12 (13.3%)		
Heart Rate	74.0 [66.0;83.0]	70.5 [65.0;82.0]	0.483	195
USD of BCA:			0.196	195
No	48 (45.7%)	32 (35.6%)		
Yes	57 (54.3%)	58 (64.4%)		
RCA, degree:			0.022	195
minor	77 (73.3%)	51 (56.7%)		
significant	28 (26.7%)	39 (43.3%)		
LAD, degree:			0.002	195
Minor	69 (65.7%)	38 (42.2%)		
Significant	36 (34.3%)	52 (57.8%)		
LCA, degree:			0.694	195
Minor	94 (89.5%)	78 (86.7%)		
Significant	11 (10.5%)	12 (13.3%)		
CA, degree:			0.001	195
Minor	84 (80.0%)	52 (57.8%)		
significant	21 (20.0%)	38 (42.2%)		
DB, degree:			0.003	195
Minor	89 (84.8%)	59 (65.6%)		
significant	16 (15.2%)	31 (34.4%)		
PIVB, degree:			0.001	195
Minor	100 (95.2%)	71 (78.9%)		
Significant	5 (4.76%)	19 (21.1%)		
IA, degree:			0.688	195
Minor	101 (96.2%)	88 (97.8%)		
significant	4 (3.81%)	2 (2.22%)		
OMB, degree:			<0.001	195
Minor	98 (93.3%)	60 (66.7%)		
Significant	7 (6.67%)	30 (33.3%)		
Number of shunts	2.00 [2.00;3.00]	3.00 [2.00;4.00]	0.001	195
Number of affected vessels	3.00 [2.00;3.00]	4.00 [4.00;5.00]	<0.001	195
Statins: Yes	105 (100%)	90 (100%)	.	195
Ezetimibe:			<0.001	195
No	101 (96.2%)	47 (52.2%)		
Yes	4 (3.81%)	**43 (47.8%)**		
Angina after CABG:			0.016	195
No	7 (6.67%)	0 (0.00%)		
Yes	98 (93.3%)	90 (100%)		

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	Therapeutic window	HRPR	p-value	N
	N=105	***N=90***		
Mortality after CABG:			0.183	195
No	104 (99.0%)	86 (95.6%)		
Yes	1 (0.95%)	4 (4.44%)		
Stenting after CABG:			<0.001	195
No	59 (56.2%)	0 (0.00%)		
Yes	46 (43.8%)	**90 (100%) !!!**		
PRU	170 [141;200]	255 [230;280]	<0.001	195
Dyslipidemia:			0.688	195
No	4 (3.81%)	2 (2.22%)		
Yes	101 (96.2%)	88 (97.8%)		
Anemia:			0.310	195
No	91 (86.7%)	83 (92.2%)		
Yes	14 (13.3%)	7 (7.78%)		
CKD:			0.689	195
No	94 (89.5%)	83 (92.2%)		
Yes	11 (10.5%)	7 (7.78%)		
Obesity:			0.462	195
No	28 (26.7%)	19 (21.1%)		
Yes	77 (73.3%)	71 (78.9%)		
RPR:			<0.001	195
Therapeutic window	105 (100%)	0 (0.00%)		
HRPR	0 (0.00%)	90 (100%)		

A total of 195 patients with a history of coronary artery bypass grafting (CABG) were included in the analysis. Based on platelet reactivity (PRU) and clinical criteria, patients were stratified into two groups: those who achieved the therapeutic window for antiplatelet therapy (n = 105) and those classified as having a high residual thrombotic risk (HRTR; n = 90). Comparative analyses of demographic, clinical, laboratory, and angiographic characteristics were performed (Table 2).

Demographic and Clinical Characteristics

No significant differences were observed between the groups regarding age (69.0 [62.0–74.0] vs. 70.5 [65.2–75.0] years; p = 0.147), sex distribution (p = 0.871), or body mass index (BMI; p = 0.096). Interestingly, the prevalence of current smoking was lower in the HRTR group compared with the therapeutic window group (27.8% vs. 43.8%; p = 0.030). Patients in the HRTR group exhibited significantly higher systolic blood pressure (130 [120–140] vs. 120 [115–130] mmHg; p = 0.031) and fasting glucose levels (5.90 [5.23–7.10] vs. 5.54 [5.00–6.20] mmol/L; p = 0.022). A prior history of stroke was also more frequent in the HRTR group (13.3% vs. 3.81%; p = 0.031).

Angiographic Findings

Patients with HRTR had more extensive coronary artery disease, with significantly higher rates of multivessel involvement. Severe stenoses were more prevalent in the proximal left anterior descending artery (57.8% vs. 34.3%; p = 0.002), left circumflex artery (42.2% vs. 20.0%; p = 0.001), diagonal branches (34.4% vs. 15.2%; p = 0.003), posterior descending artery (21.1% vs. 4.76%; p = 0.001), and venous bypass grafts (33.3% vs. 6.67%; p < 0.001). Furthermore, the HRTR group had a higher number of diseased vessels (4.00 [4.00–5.00] vs. 3.00 [2.00–3.00]; p < 0.001) and bypass grafts (3.00 [2.00–4.00] vs. 2.00 [2.00–3.00]; p = 0.001).

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Platelet Reactivity and Clinical Outcomes

Platelet reactivity was markedly elevated in the HRTR group (PRU: 255 [230–280] vs. 170 [141–200]; $p < 0.001$), indicating a suboptimal response to dual antiplatelet therapy. Consistently, all patients in the HRTR group underwent post-CABG stenting (100% vs. 43.8%; $p < 0.001$) and experienced recurrent angina (100% vs. 93.3%; $p = 0.016$).

Medical Therapy

All patients were treated with statins; however, ezetimibe was prescribed significantly more often in the HRTR group (47.8% vs. 3.81%; $p < 0.001$), reflecting attempts at intensified lipid-lowering therapy.

Summary of Findings

Patients classified as HRTR exhibited:
More extensive and severe coronary atherosclerosis;
Higher platelet reactivity despite dual antiplatelet therapy;
Increased frequency of recurrent angina and need for repeat revascularization;
Greater use of adjunctive lipid-lowering therapy.
These findings emphasize the role of HRTR as a marker of poor outcomes in post-CABG patients and underscore the importance of individualized antiplatelet and lipid-lowering strategies in this high-risk population.

Table 3. Stepwise logistic regression: predictors associated with the risk of developing stenting after CABG.

		HRPR	
Predictors	**Odds Ratios**	**CI**	**p**
Number of affected vessels	52.67	17.33 – 213.77	**<0.001**
TSH	0.87	0.72 – 1.00	0.116
Ezetimibe: Yes	0.12	0.02 – 0.75	**0.023**
Potassium	2.53	0.78 – 8.59	0.127
Hb A 1 c	1.18	0.95 – 1.46	0.138
Observations		195	
R^2 Tjur		0.681	

A stepwise logistic regression analysis was performed to identify predictors associated with the risk of stenting after coronary artery bypass grafting (CABG). Due to the relatively small sample size (n = 195) and a large number of potential covariates, a stepwise forward/backward selection algorithm was employed (table 3, picture 1).

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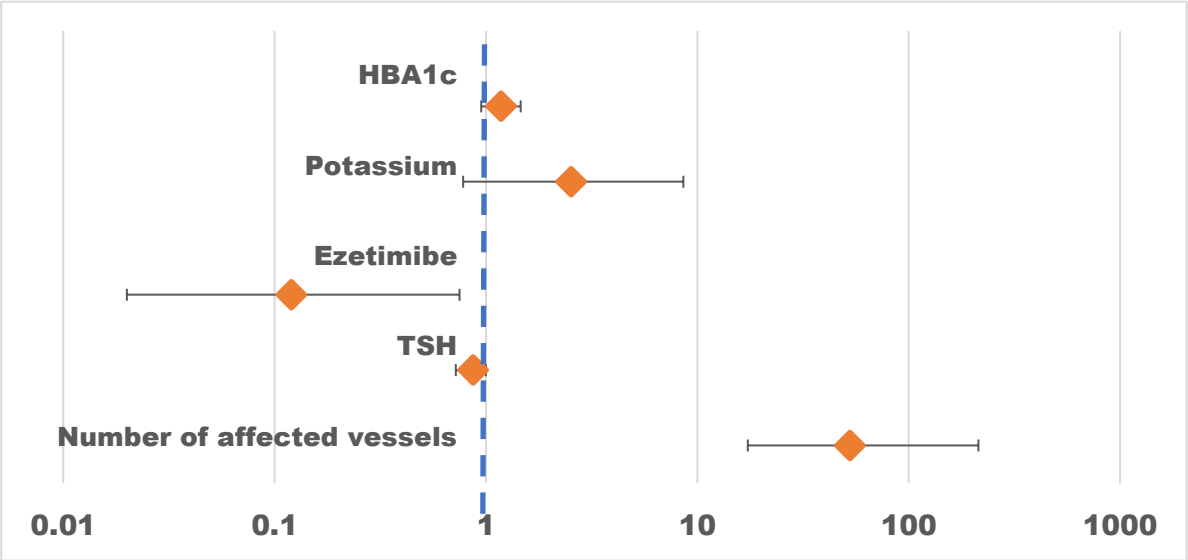

Figure 2. Stepwise logistic regression: predictors associated with the risk of developing stenting after CABG.

Among the variables included in the regression analysis, the **number of affected vessels** emerged as the strongest and statistically significant predictor of post-CABG stenting. Patients with more extensive coronary involvement had markedly higher odds of requiring stent implantation (Odds Ratio [OR] = 52.67; 95% CI: 17.33–213.77; $p < 0.001$).

Conversely, the **use of ezetimibe** was independently associated with a significantly lower risk of stenting (OR = 0.12; 95% CI: 0.02–0.75; $p = 0.023$), suggesting a potential protective effect of this lipid-lowering therapy in the postoperative setting.

Other factors, including thyroid-stimulating hormone (TSH) levels (OR = 0.87; 95% CI: 0.72–1.00; $p = 0.116$), serum potassium (OR = 2.53; 95% CI: 0.78–8.59; $p = 0.127$), and glycated hemoglobin (HbA1c) (OR = 1.18; 95% CI: 0.95–1.46; $p = 0.138$), did not reach statistical significance but were retained in the final model as clinically relevant covariates.

The regression model demonstrated good explanatory power, with a Tjur's R^2 of 0.681, indicating that a substantial proportion of the variance in stenting risk was explained by the selected predictors.

Collectively, these findings emphasize the critical role of disease burden in determining the need for repeat revascularization, while also highlighting the potential benefit of ezetimibe as part of intensified secondary prevention strategies in post-CABG patients.

DISCUSSION

Our study highlights the substantial burden of recurrent ischemia and the high rate of re-intervention among post-CABG patients in a real-world clinical setting. Recurrent ischemic symptoms were observed in 94% (n = 188) of patients, with 68% requiring repeat PCI. These findings reflect the ongoing progression of atherosclerosis and/or incomplete revascularization, underscoring the challenges of long-term secondary prevention in this population. The role of platelets in arterial thrombosis is well established, particularly in patients with coronary heart disease (CHD) who are on antiplatelet therapy, which has been shown to reduce the risk of major adverse cardiovascular events. Hemoglobin levels also serve as a critical prognostic marker in patients with chronic heart failure (CHF), where anemia is a frequent comorbidity and is associated with increased risks of hospitalization and mortality [2]. Patients with HRPR who undergo percutaneous coronary intervention (PCI) with stent placement while receiving clopidogrel therapy are at elevated risk for recurrent ischemic events. Notably, residual platelet reactivity and HRPR levels have been found to increase in parallel with declining kidney function [3]. Smoking, a well-known risk factor for CHD and MI, is also strongly associated with increased platelet reactivity. When combined with HRPR,

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smoking further elevates the risk of stent thrombosis [4]. Dyslipidemia contributes to heightened platelet reactivity and thrombotic risk. Elevated cholesterol levels are known to enhance platelet activation and aggregation [5]. Similarly, the extent of coronary atherosclerosis correlates positively with platelet reactivity, suggesting that increased HRPR reflects more widespread atherosclerotic involvement [6]. Anemia has been shown to impair responsiveness to clopidogrel, thus contributing to elevated HRPR [7], while renal dysfunction is also independently associated with increased platelet reactivity [8]. HRPR is recognized as a poor prognostic marker in acute coronary syndrome (ACS) [9]. Moreover, grade 1 obesity has been linked to higher HRPR in patients undergoing antiplatelet therapy [10]. In patients undergoing CABG, alterations in the hemostatic system due to cardiopulmonary bypass may further contribute to increased platelet reactivity [11]. The primary association between HRPR and cardiovascular risk is mediated through enhanced platelet activation, which accelerates thrombus formation [12]. HRPR is therefore regarded as an independent risk factor for a range of serious complications, including myocardial infarction, stent thrombosis, and cardiovascular death [13]. Platelets are directly involved in thrombus formation following the rupture of atherosclerotic plaques in the coronary arteries [14], and individuals with HRPR are at significantly higher risk of recurrent ischemic events [15].

Despite adherence to the 2024 European Society of Cardiology (ESC) guidelines for the management of chronic coronary syndromes, a considerable proportion of patients continued to experience ischemic symptoms. This suggests the persistence of residual risk factors, including dyslipidemia and high platelet reactivity, as well as difficulties in achieving recommended LDL-C targets.

A key driver of recurrent ischemia was persistent **dyslipidemia**, with most patients failing to reach LDL-C goals despite statin therapy. Limited access to more potent lipid-lowering therapies (e.g., ezetimibe, PCSK9 inhibitors) further contributed to this gap. In Kazakhstan, these medications are not included in the national reimbursement list and are therefore not provided free of charge, which likely explains the underutilization of combination lipid-lowering therapy and the near-universal failure to achieve LDL-C targets [16].

Another important finding was the high prevalence of **residual platelet reactivity**, as measured by aggregometry in patients receiving dual antiplatelet therapy. This phenotype is known to be associated with increased thrombotic risk, recurrent ischemia, and a higher likelihood of stent failure, which is consistent with our observation of frequent post-CABG revascularization. In addition, comorbid conditions such as anemia, chronic kidney disease, and heart failure were common and likely amplified residual cardiovascular risk. These results are in line with previous reports demonstrating that non-cardiac comorbidities significantly impair long-term outcomes after surgical revascularization. Taken together, our findings point to distinct **clinical phenotypes**—such as dyslipidemic-thrombotic or cardio-renal-anemic—that may benefit from individualized post-operative management rather than uniform treatment protocols. This approach is particularly relevant in underrepresented regions such as Central Asia, where healthcare resource limitations further complicate secondary prevention.

LIMITATIONS

This study has several limitations. First, it was a retrospective, single-center analysis conducted at the National Research Institute of Cardiology and Internal Medicine, Almaty, Kazakhstan. Although patients were referred from diverse regions, many represented complex or refractory cases of coronary artery disease. Consequently, the findings may not be generalizable to the broader post-CABG population, especially those with less severe clinical presentations or treated at primary-level facilities. Additionally, key parameters such as inflammatory biomarkers or genetic determinants of platelet resistance were not consistently available due to real-world practice constraints.

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CONCLUSIONS

Residual dyslipidemia and platelet hyperreactivity remain prevalent and clinically significant contributors to recurrent ischemia and repeat revascularization after CABG. Patients requiring repeat PCI had more extensive coronary involvement, elevated platelet reactivity reflecting suboptimal antiplatelet response, and were more frequently prescribed intensified lipid-lowering therapy. Importantly, the extent of vascular disease and ezetimibe use emerged as independent predictors of stenting risk. These results underscore the need for **personalized strategies** in lipid-lowering and antiplatelet therapy to optimize outcomes in this high-risk population. Tailored phenotype-guided approaches are especially critical in Kazakhstan, where limited access to advanced therapies may exacerbate residual risk and impede secondary prevention efforts.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figure S1. The flow chart of patients; Figure S2: Stepwise logistic regression: predictors associated with the risk of developing stenting after CABG; Table S1: Descriptive statistics of the group without re-stenting and with re-stenting; Table S2: Descriptive statistics of the Therapeutic window/HRPR group; Table S3: Stepwise logistic regression: predictors associated with the risk of developing stenting after CABG.

Author Contributions:. Conceptualization, A.M., L.D., Sh.Zh, F.N., D.K. and A.S; methodology, A.M., L.D., Sh.Zh, F.N., D.K. and A.S.; formal analysis, A.M., Sh.Zh, F.N., D.K., A.S., O.S., F.R. and D.A.; in-vestigation, A.M., Sh.Zh, F.N., D.K., O.S., F.R. and D.A.; resources, A.M., Sh.Zh., D.K., F.N., O.S. and D.A.; data curation, A.M., Sh.Zh., F.N., D.K. and D.A.; writing—original draft, A.M., Sh.Zh., F.N., D.K., O.S., D.A. and A.S.; writing—review and editing, A.M., F.N., O.S., D.K. and F.R..; visualization, L.D., Sh.Zh., D.K., F.N., O.S., F.R., and D.A; supervision, A.M., L.D. and Sh.Zh. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declara-tion of Helsinki, and approved by the Local Ethics Committee of Asfendiyarov Kazakh national medical university, Almaty, Republic of Kazakhstan (protocol code 11(134), date of approval 04.11.2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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Abbreviations

The following abbreviations are used in this manuscript:

ACS	Acute coronary syndrome
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CA	Circumflex artery
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CHF	Congestive heart failure
CRP	C-reactive protein
CVDs	Cardiovascular diseases
DB	Diagonal branch
DBP	Diastolic blood pressure
EDD	End-diastolic dimension
EDV	End-diastolic volume
EF	Election fravtion
ESD	End-systolic dimension
ESV	End-systolic volume
GFR	Glomerular filtration rate
HRPR	High residual platelet reactivity
IA	Intermediate artery
IHD	Ischemic heart disease
IVS	Intraventricular septum
LA	Left atrium
LAD	Left anterior descending
LCA	Left coronary artery
LD	Linear dichroism
LDL-C	Low-density lipoprotein cholesterol
LV	Left ventricular
LVPW	Left ventricular posterior wall
MACE	Major Adverse Cardiovascular Events
OMB	Obtuse marginal branch
PIVB	Posterior interventricular branch
RCA	Right coronary artery
RPR	Residual platelet reactivity
RV	Right ventricular
SBP	Systolic blood pressure
sPAP	Systolic pulmonary artery pressure
SV	Stroke volume
TG	Tryglicerides
MV	Mitral Valve
TV	Tricuspid Valve
AV	Aortic Valve
AH	Arterial Hypertension
TSH	thyroid-stimulating hormone
USD BCA	Ultrasound of Brachiocephalic Arteries

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