THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Evaluation of Whole Blood Viscosity to Predict Stent Restenosis in Patients with Coronary Artery Disease

ABSTRACT

Background: This study investigated the relationship between whole blood viscosity (WBV) and in-stent restenosis (ISR) in patients with prior coronary stent implantation who underwent coronary angiography (CAG) for chronic coronary syndrome (CCS).

Methods: In this retrospective case-control study, 802 patients who underwent CAG with suspected ISR were included. In-stent restenosis was defined as ≥50% stenosis within the stent or within 5 mm of its edges. Patients were divided into an ISR group (n = 342) and a control group without ISR (n = 460). Whole blood viscosity was calculated using both high-shear rate viscosity (HSR) and low-shear rate viscosity (LSR).

Results: Whole blood viscosity levels were significantly higher in the ISR group for both HSR (16.8 ± 1.0 vs. 15.6 ± 0.9 cP, *P* < .001) and LSR (83.1 ± 8.4 vs. 80.8 ± 8.0 cP, *P* < .001). Receiver-operating characteristic curve (ROC) analysis showed strong predictive power for ISR (area under the curve [AUC] 0.84 for LSR and 0.82 for HSR). Kaplan–Meier analysis demonstrated significantly lower ISR-free survival in patients with high WBV (*P* < .001). Multivariate Cox regression identified both HSR and LSR as independent predictors of ISR.

Conclusion: Increased WBV is independently linked to ISR and may contribute to its development via endothelial inflammation and vascular remodeling. Whole blood viscosity demonstrates potential utility as a biomarker for the identification of CCS patients susceptible to ISR.

Keywords: Chronic coronary syndrome, coronary angiography, in-stent restenosis, percutaneous coronary interventions, whole blood viscosity

ORIGINAL INVESTIGATION

INTRODUCTION

The leading global cause of death is coronary artery disease (CAD), which results mainly from atherosclerosis. Progress in both the diagnosis and treatment of CAD has led to enhanced management strategies, with an emphasis on modifying risk factors through medical therapy, percutaneous coronary interventions (PCI), and coronary artery bypass grafting (CABG).[1] Percutaneous coronary intervention, employing balloon angioplasty with bare-metal stents (BMS) or drug-eluting stents (DES), constitutes the most prevalent revascularization method.[2] The advancement of PCI commenced with balloon angioplasty and has progressed through subsequent generations of DES, integrating increasingly sophisticated stent technologies.[3] Despite the widespread adoption of PCI, limitations exist due to the rising incidence of in-stent restenosis (ISR), a reaction to vascular injury associated with stent use.[4]

Whole blood viscosity (WBV) is defined as the internal resistance of blood flow in the vessels. Whole blood viscosity is the primary marker of endothelial shear stress and has emerged as a significant predictor of cardiovascular diseases (CVD). Various studies have demonstrated the relationship between WBV and CAD and its prognostic importance.[5,6] At the same time, WBV is associated with traditional cardiovascular risk factors, such as hypertension, hyperlipidemia, metabolic syndrome, and diabetes.[5,6]

Copyright@Author(s) - Available online at anatoljcardiol.com.
Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Yunus Çalapkulu[1]
Mehmet Erdoğan[2]
Abdullah Nabi Aslan[3]
Nihal Akar[2]
Serkan Bulguroğlu[4]
Burak Kardeşler[5]
Mehmet Akif Erdöl[5]

[1]*Department of Cardiology, University of Health Sciences, Ankara Mamak State Hospital, Ankara, Türkiye*
[2]*Department of Cardiology, Ankara Yıldırım Beyazıt University Medical School, Ankara, Türkiye*
[3]*Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates*
[4]*Department of Cardiology, University of Health Sciences, Hatay Dörtyol State Hospital, Hatay, Türkiye*
[5]*Department of Cardiology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye*

Corresponding author:
Yunus Çalapkulu
✉ yunuscalapkulu@gmail.com

Received: March 11, 2025
Accepted: May 6, 2025
Available Online Date: May 26, 2025

Cite this article as: Çalapkulu Y, Erdoğan M, Aslan AN, et al. Evaluation of whole blood viscosity to predict stent restenosis in patients with coronary artery disease. *Anatol J Cardiol.* 2025;29(9):503-511.

DOI:10.14744/AnatolJCardiol.2025.5407

In routine clinical practice, direct measurement of WBV is limited by the technical equipment requirement and the lack of standardization regarding the measurement. De Simone et al[7] showed that WBV can be calculated at desired shear rates with a formula based on plasma protein concentration and hematocrit (HCT) values, which are the components of WBV. There is currently no study in the literature on the effects of WBV on predicting stent restenosis in chronic coronary syndrome (CCS) patients with coronary stents. Within the scope of this research, the aim was to evaluate the relationship between WBV and stent restenosis in patients with a history of previous coronary stents who underwent coronary angiography (CAG) because of CCS and in whom coronary angiography (CAG) revealed ISR. The primary endpoint of this study was to determine the positive relationship between WBV and stent restenosis in patients with CCS and to evaluate the importance of WBV in predicting stent restenosis and its power in detecting the disease.

METHODS

This observational, retrospective case-control study included 802 patients who applied to a specialized cardiovascular hospital and underwent CAG with a preliminary diagnosis of CCS because of ISR. All procedures adhered to the ethical standards stipulated by both the institutional and national review boards, consistent with the 2008 revision of the Helsinki Declaration of 1975. The institution has granted ethics committee approval with protocol number E1-22-2779. As this was a retrospective study, no informed consent was obtained from the participants.

In-stent restenosis was diagnosed via coronary angiography. In-stent restenosis was accepted if there was over 50% stenosis inside the stent or up to 5 mm of its proximal and distal edges.[8] The study included 802 patients. Of these, 342 were assigned to the restenosis group based on established criteria, with the remaining 460 patients forming the control group.

Demographic data of patients included in the study were collected from patient files, medical pharmacy data, and e-pulse system, which were scanned retrospectively and added to the follow-up form. Angiography images and reports related to the patient's previously implanted stents were recorded. In addition, CAG images performed within the current indication in the hospital were viewed, and information about the stent and the procedures performed were reported. Patients were called by phone to obtain the necessary information when information could not be obtained.

The patients' complete blood count (CBC) and biochemical parameters were taken from a wide antecubital vein after 12 hours of fasting in the morning before the patients came to the angiography laboratory. Sysmex K-1000 (Sysmex Corporation, Kobe, Japan) for CBC and COBAS C-501 (Roche, Manheim, Germany) devices for biochemical parameters are used in the hospital's biochemistry laboratory. Blood samples are placed in standard ethylenediamine tetraacetic acid (EDTA) tubes for total CBC tests, and measurements are performed immediately after blood collection. Serum C-reactive protein (CRP) levels are measured by immune nephelometry (NFL BN-II, Siemens Dade Behring). The CRP cut-off value was determined as 0-0.005 g/L.

Whole blood viscosity, HCT (%), and plasma protein concentration (g/L) were calculated for both LSR (low shear rate 0.5 s –1) and HSR (high shear rate 208 s –1) using the validated formulas of De Simone et al[7] Several studies have indicated that the best method for estimating LSR WBV is by incorporating HCT as a percentage and total protein as grams per liter in the calculation.[9] Tamariz et al[10] offer a precise definition of these calculations; therefore, the calculations were conducted in accordance with this definition:

- HSR (208 s –1) = (0.12 × HCT) + 0.17 (total protein –2.07)
- LSR (0.5 s –1) = (1.89 × HCT) + 3.76 (total protein –78.42)

The writing process involved AI and AI-assisted tools like Grammarly and MS Word Editor. While these technologies enhanced the clarity and style of the work, they did not supplant core authorial functions, including the generation of scientific or medical understanding, the formulation of scientific conclusions, and the provision of clinical advice.

Study Participants

This retrospective analysis has enrolled patients aged ≥ 18 who had previously undergone CAG and PCI with a stent in at least 1 artery and individuals who underwent CAG due to CCS. Study exclusion criteria included acute coronary syndrome, symptomatic heart failure with left ventricular ejection fraction under 40%, congenital heart disease, and severe valvular heart disease, as assessed via echocardiography. Moreover, participants with advanced liver disease (diagnosed cirrhosis) or chronic kidney disease (GFR <30 mL/min/1.73 m^2) were excluded from the study. Participants with a body mass index (BMI) exceeding 45 kg/m^2, a family history of dyslipidemia, or suspected familial hypertriglyceridemia (plasma triglycerides > 500 mg/dL [5.65 mmol/L] or ≥1 first-degree relative with triglycerides ≥500 mg/dL) were excluded. Subjects with a history of cancer, autoimmune disorders, connective tissue disorders, or active infection were also excluded from this study.

HIGHLIGHTS

- Independent associations were found between whole blood viscosity (WBV) (at both high and low shear rates) and in-stent restenosis (ISR) among patients with a history of coronary artery stent placement who underwent angiography for chronic coronary syndrome.
- The predictive power of WBV for ISR was evident in ROC curve analyses, which displayed an Area Under the Curve of 0.84 for low shear rate and 0.82 for high shear rate, highlighting its potential as a trustworthy biomarker.
- Multivariate Cox regression showed that WBV, smoking status, stent type, length, and diameter were independent predictors of ISR. The analysis particularly highlighted WBV as a significant, measurable risk factor readily applicable in clinical settings.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM SPSS for Windows 26.0 (IBM Corp., Armonk, NY, USA) package program. Data distribution was performed using the Kolmogorow-Smirnov test, histogram curves, skewness/kurtosis values, coefficients of variation, and detrended Q-Q plot data. Student's *t*-test was applied in comparing 2 independent numerical variable groups with normal distribution, and data were presented as mean ± SD. The Mann–Whitney *U* test was used to compare 2 independent numerical variables without normal distribution, and data were presented as median (25^{th}-75^{th} quartiles). In comparing 2 independent categorical variables, chi-square or Fisher's Exact test was applied according to the suitability of the assumptions, and data were presented as numbers (%).

ROC curve analysis was performed to predict stent restenosis and to determine the cut-off values of HSR and LSR levels. In addition to sensitivity and specificity, the area under the ROC curve (AUC) was presented with a 95% confidence interval (CI).

According to the predictive values obtained from the ROC curve, groups were dichotomized as high and low whole blood velocity. The predictive value for HSR was 16.21 cP, and for LSR, it was 81.90 cP. Then, cumulative risk ratios were calculated using the Kaplan-Meier method, and the groups with low and high whole blood velocity were compared for both HSR and LSR using the log-rank test. Then, Cox proportional hazard regression analysis was performed to determine the independent predictors for restenosis.

In the first stage, clinical, demographic, laboratory, and procedural parameters, including WBV parameters thought to be/may be associated with stent restenosis, were applied to the univariate Cox regression model. Then, parameters reaching statistical significance ($P < .1$) in univariate analysis were included in multivariate analysis to determine independent predictors of restenosis. Multivariate Cox regression analyses were performed in 2 separate models to evaluate whether HSR (Model 1) and LSR (Model 2) were independent predictors of restenosis. Regression analysis presented data with a 95% CI and hazard ratio (HR).

Kaplan–Meier analysis was employed to assess cumulative ISR incidence, categorizing participants into high and low blood viscosity groups according to a cutoff point established via ROC analysis. Kaplan-Meier curves for ISR-free survival were constructed for HSR and LSR viscosity groups. Differences between the survival curves were compared using the log-rank test. Survival data were analyzed according to event time (in months) and restenosis status (event or censored). Two-sided *P* values less than .05 were considered significant for all statistical analyses.

RESULTS

The study included 802 patients with angiography due to CCS, previous CAG and percutaneous coronary intervention, and a stent in at least 1 artery. The mean age of the study patients was 63 ± 10 years, the minimum age was 37, and the maximum age was 89, and 75% of these patients (n = 599) were male.

Table 1. Demographic Characteristics and Comorbidities of the Study Population

Variables	n = 802
Age, years (mean ± SD)	63 ± 10
Gender, male, n (%)	599 (75)
Diabetes, n (%)	339 (42)
Hypertension, n (%)	567 (71)
Dyslipidemia, n (%)	231 (29)
Smoking, n (%)	217 (27)
Chronic obstructive pulmonary disease, n (%)	24 (3)
Chronic kidney disease, n (%)	132 (16)

The demographic characteristics of the study population are denoted in Table 1. Diabetes mellitus was detected in 339 (42%) of the study population, hypertension in 567 (72%), and dyslipidemia in 231 (29%). It was determined that 89% (n = 713) of the patients participating in the study used acetylsalicylic acid, 81% (n = 648) beta-blockers, and 77% (n = 619) statins.

In the patient group with ISR, 201 (59%) patients only received percutaneous transluminal coronary angioplasty (PTCA) in the stent. In addition, 77 (22%) of these patients underwent coronary stenting after PTCA. In addition, 43 (13%) of these patients were treated with CABG, and 78 (23%) were followed up with only medical treatment. Baseline demographic information of the groups with (≥50%) and without (<50%) ISR is presented in Table 2.

The coronary artery where the stent was first placed significantly differed between the restenosis and non-restenosis groups ($P = .009$). The type of the first stent implanted was significant between the restenosis and non-restenosis groups ($P = .026$). The length of the first stent was determined as a median of 28 mm (23-33 mm) in the restenosis group and a median of 23 mm (18-28 mm) in the non-restenosis group, and a significant difference was found between the 2 groups ($P < .001$). The diameter of the first stent implanted in the ISR group was smaller than in the non-restenosis control group (2.96 ± 0.37 mm vs. 3.02 ± 0.39 mm, respectively, $P = .030$). The median time after the first stenting in the ISR group was 61 months (35-88 months), while the median time in the non-restenosis group was 40 months (24-68 months), and a statistically significant difference was found between these 2 groups ($P < .001$).

In the group with restenosis, the predictive values of patient characteristics and laboratory parameters for stent restenosis were evaluated by ROC curve analysis (Table 3). The predictive (cut-off) values for glucose 102.5 mg/dl with 60% sensitivity and 58% specificity (AUC 0.61; 95% CI, 0.57-0.65; $P < .001$), time since first stent implantation 47.6 months with 64% sensitivity and 57% specificity (AUC 0.63; 95% CI, 0.59-0.66; $P < .001$) and stent length 23.5 with 60% sensitivity and 67% specificity (AUC 0.67; 95% CI, 0.63-0.71; $P < .001$) predicted stent restenosis. When the predictive value for LSR is taken as 40.04 cP, it predicted stent restenosis with 80% sensitivity and 76% specificity (AUC 0.84; 95% CI, 0.81-0.87; $P < .001$), and when the predictive value for HSR is taken as 16.21

Table 2. Comparison of Baseline Characteristics of Groups with In-Stent Restenosis (≥50% stenosis) and Without (<50%)

	Restenosis (n = 460)	No Restenosis (n = 342)	*P*
Demographic characteristics			
Age, years (mean ± SD)	62±10	63±10	.574
Sex, male, n (%)	330 (72)	269 (78)	.026
Comorbidities			
Diabetes, n (%)	188 (41)	151 (44)	.352
Hypertension, n (%)	316 (69)	251 (73)	.148
Dyslipidemia, n (%)	125 (27)	106 (31)	.237
Smoking, n (%)	81 (18)	136 (40)	<.001
Chronic obstructive pulmonary disease, n (%)	13 (3)	11 (3)	.748
Chronic kidney disease, n (%)	76 (16)	56 (16)	.956
Current medications			
Acetyl salicylic acid, n (%)	412 (90)	301 (88)	.488
P2Y12 inhibitor, n (%)	115 (25)	65 (19)	.044
Beta blocker, n (%)	385 (84)	263 (77)	.016
RAAS, n (%)	332 (72)	244 (71)	.796
Statin, n (%)	367 (80)	252 (74)	.042

RAAS: Renin-Angiotensin-Aldosterone System

cP, it predicts stent restenosis with 78% sensitivity and 75% specificity (AUC 0.82; 95% CI, 0.79-0.85; *P* < .001) (Figure 1).

According to the predictive values obtained from the ROC curve (the predictive value for HSR is 16.21 cP, and the predictive value for LSR is 40.04 cP), groups were dichotomized as high and low WBV. Cumulative risk ratios for LSR and HSR were given to these groups using the log-rank test with the Kaplan-Meier method. In Kaplan–Meier analysis, high WBV calculated by HSR and LSR had a higher cumulative risk for stent restenosis than low blood viscosity (Log-rank test, *P* < .001).

Clinical, demographic, laboratory, and procedural parameters were evaluated with time-dependent Cox-regression analysis, including WBV parameters thought to be or may be associated with stent restenosis (separately for HSR and LSR). In the Cox regression model including multivariate HSR, smoking (HR: 1.63, 95% CI: 1.30-2.06, *P* < .001), first implanted stent type (HR: 2.26, 95% CI: 1.22-4.16, *P* = .009), stent length (HR: 1.02, 95% CI: 1.01-1.03, *P* < .001), stent diameter (HR: 0.55, 95% CI: 0.37-0.81, *P* = .002) and HSR-calculated WBV (HR: 1.48, 95% CI: 1.33-1.65, *P* < .001) were determined as independent predictors of stent restenosis (Table 4). In the multivariate Cox regression model including LSR, smoking (HR: 1.62, 95% CI: 1.29-2.04, *P* < .001), type of first implanted stent (HR: 2.24, 95% CI: 1.21-4.12, *P* = .010), stent length (HR: 1.02, 95% CI: 1.01-1.03, *P* < .001), stent diameter (HR: 0.55, 95% CI: 0.37-0.81, *P* = .002) and LSR-estimated WBV (HR: 1.02, 95% CI: 1.01-1.03, *P* < .001) were determined as predictors of stent restenosis.

Kaplan–Meier analysis revealed a statistically significant disparity in ISR-free survival among patients categorized by HSR. Results from the log-rank test demonstrated a statistically significant association between high HSR levels and an elevated risk of ISR ($\chi^2 = 6.94$, df = 1, *P* = .008). The high HSR group exhibited a higher-than-anticipated ISR event count (observed: 377, expected: 414), suggesting reduced ISR-free survival probability (Figure 2). In a similar vein, patients with increased LSR showed significantly poorer ISR-free

Table 3. Predictive Values of Patient Characteristics and Laboratory Parameters for Stent Restenosis in the Group with Restenosis

Risk Factors	AUC (95%)	Predictive Value	Hazard Ratio	Sensitivity (%)	Specificity (%)	*P*
Glucose	0.61 (0.57-0.65)	102.5	1.43	60	58	<.001
Creatine	0.55 (0.51-0.59)	0.90	1.09	52	53	.018
LDL-C	0.56 (0.52-0.60)	86.5	1.24	60	51	.003
HDL-C	0.47 (0.43-0.51)	38.5	0.91	47	49	.109
Triglyceride	0.55 (0.51-0.59)	140.5	1.14	60	57	.008
HSR	0.82 (0.79-0.85)	16.21	3.10	78	75	<.001
LSR	0.84 (0.81-0.87)	40.04	3.38	80	76	<.001
Time since first stenting	0.63 (0.59-0.66)	47.6	1.49	64	57	<.001
Stent length	0.67 (0.63-0.71)	23.5	1.81	60	67	<.001
Stent diameter	0.47 (0.43-0.51)	2.88	0.96	64	43	.099

AUC, area under the curve; HDL-C, high-density lipoprotein cholesterol; HSR, whole blood viscosity at high shear rate (208/sec); LDL-C, low-density lipoprotein cholesterol; LSR, whole blood viscosity at low shear rate (0.5/sec).

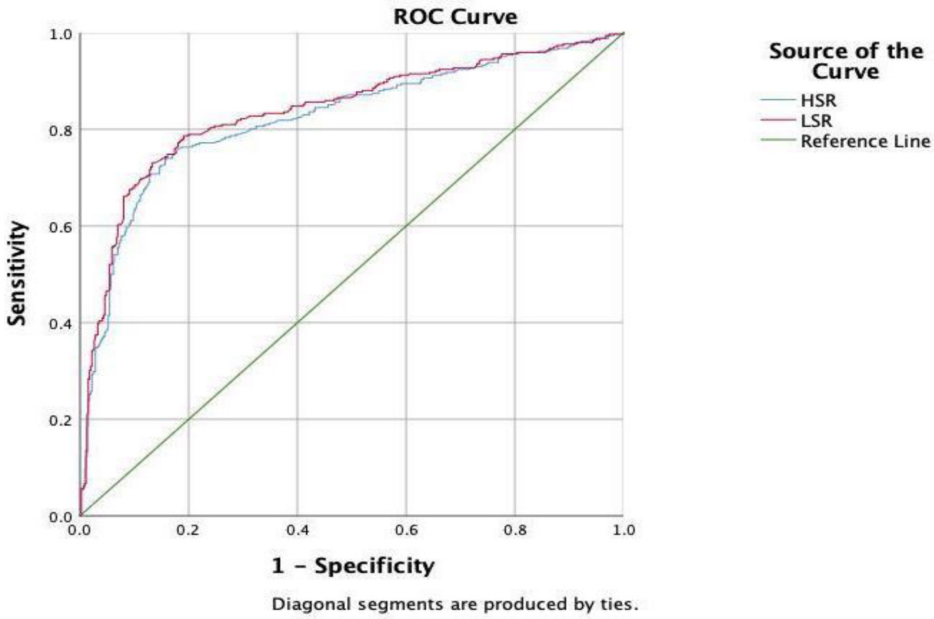


Figure 1. ROC curve analysis of high shear rate and low shear rate levels for prediction of stent restenosis.

survival. Analysis using the log-rank test demonstrated a statistically significant difference between LSR groups (χ^2 = 5.97, df = 1, *P* = .014). In the high LSR group, the observed number of ISR events (n = 383) surpassed the expected number (n = 417), thus reinforcing the link between increased LSR and heightened restenosis risk (Figure 3).

DISCUSSION

Of the 802 patients in this study, 342 were CKS patients who had previously received a stent and developed restenosis after an average of 61 months. WBV calculated with both LSR and HSR was significantly higher in this restenosis group than in the group without restenosis. In addition, WBV calculated with LSR and HSR was found to be an independent predictor of stent restenosis. It was determined that WBV could predict stent restenosis with 80% sensitivity and 76% specificity when the predictive value was taken as 40.04 cP for LSR and with 78% sensitivity and 75% specificity when the predictive value of HSR was taken as 16.21 cP. In addition, in separate multivariate Cox regression analyses including LSR and HSR, smoking and stent diameter, length, and type were independent predictors of ISR. This is the first study in the literature to investigate the relationship between ISR and WBV.

To delay the progression of coronary atherosclerosis and prevent its adverse outcomes, in addition to risk factor

Table 4. Univariate and Multivariate Cox Regression Analysis of Stent Restenosis (Model Generated with HSR)

	Univariate			Multivariate#		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	0.98	0.97-0.99	.002	0.99	0.99-1.01	.906
Gender	0.85	0.66-1.11	.237	–	–	–
Diabetes	1.03	0.83-1.28	.761	–	–	–
Hypertension	1.18	0.93-1.50	.179	–	–	–
Smoking	2.03	1.63-2.53	<.001	1.63	1.30-2.06	<.001
LDL-C	0.99	0.99-1.00	.649	–	–	–
HDL-L	0.99	0.98-1.00	.288	–	–	–
Triglyceride	1.01	1.00-1.01	.026	1.00	0.99-1.01	.781
Statin	1.20	0.94-1.52	.144	–	–	–
Creatinine	1.31	0.84-2.05	.233	–	–	–
Stent type (BMS vs DES)	1.61	0.96-2.71	.073	2.26	1.22-4.16	.009
Stent length	1.03	1.02-1.04	<.001	1.02	1.01-1.03	<.001
Stent diameter	0.66	0.48-0.92	.013	0.55	0.37-0.81	.002
HSR	1.61	1.45-1.78	<.001	1.48	1.33-1.65	<.001

BMS, bare metal stent; CI, confidence interval; DES, drug-eluting stent; HDL-C, high-density lipoprotein cholesterol; HR, Hazard ratio; HSR, Whole blood viscosity at high shear rate (208/s); LDL-C=low-density lipoprotein cholesterol.
#Chi square value of multivariate Cox regression model: 129; –2 Log likelihood: 3611; *P* < .001.

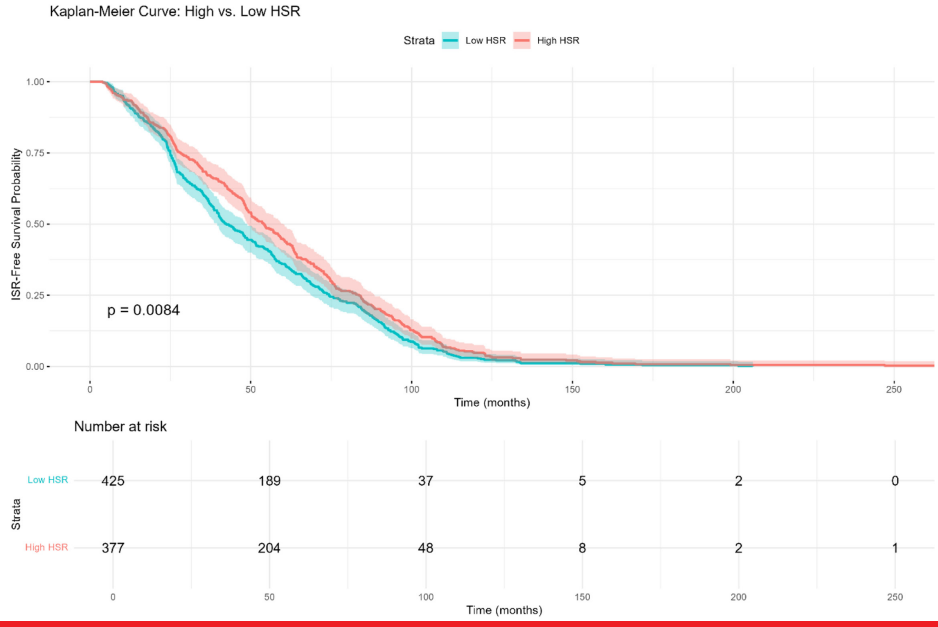


Figure 2. Kaplan–Meier estimates of in-stent restenosis–free survival stratified by high-shear rate blood viscosity.

modification, methods such as medical treatment, PCI, and CABG are currently applied.[3] Percutaneous coronary intervention started in the 1980s with balloon angioplasty as an alternative to CABG and later continued its development with the introduction of BMS and DES.[11] Although PCI is widely used, restenosis, which is the response of the stent-bearing vessel to trauma, reduces the long-term success of this method. Although the use of DES, in particular, has reduced the incidence of ISR, it remains a significant problem today.[12]

Mechanical tension after stent implantation activates a series of inflammatory mechanisms. Inflammation at the cellular level that develops in ISR is the most critical part of the restenosis process. This inflammation causes the proliferation of smooth muscle cells. At the end of this process, neointimal hyperplasia and neoatherosclerosis are inevitable.[13] Clinical predictors of ISR include diabetes, chronic kidney disease, advanced age, male gender, and high BMI.[14]

Endothelial shear stress (ESS) is a critical hemorheological element for the development and progression of atherosclerosis. Whole blood viscosity, a marker of ESS, plays a vital role in maintaining the functionality of the endothelium. As it is known, high blood viscosity causes turbulent flow in the lumen and does not allow the blood to flow regularly. This

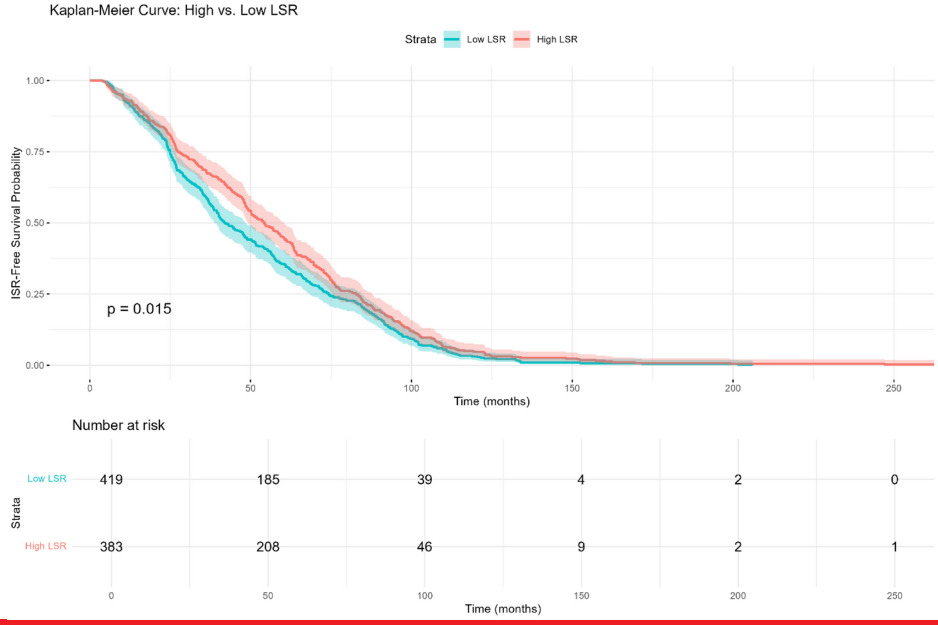


Figure 3. Kaplan–Meier estimates of in-stent restenosis–free survival stratified by low-shear rate blood viscosity.

situation increases endothelial deterioration and disrupts integrity.[15] This situation has provided a new perspective for other studies and this study. The effect of WBV on blood flow is not linear. A moderate viscosity increase helps maintain the normal endothelium function by increasing vasodilator substances such as nitric oxide from the endothelium. In contrast, a high rise in viscosity does not increase the production of additional vasodilators via mechanotransduction, which causes endothelial dysfunction. Some studies have proven that high blood viscosity plays a role in vascular remodeling and endothelial inflammation.[16,17] Another accepted mechanism is that in patients with high blood viscosity, leukocytes and platelets were found in higher numbers in the areas of the vascular wall, which are essential for adhesion and aggregation. This situation promotes the infiltration of cholesterol particles and substances that increase the development of atherosclerosis, such as fibrinogen, into the vascular wall. This idea has been proven by studies that there is a relationship between blood rheology and the formation of atherosclerosis in the carotid and coronary arteries.[18]

Yagi et al[19] investigated the relationship between blood rheology and endothelial function using flow-related vasodilation of the brachial artery, an indicator of endothelial function. As a result, a relationship was found between hemorheology and flow-related vasodilation. Consequently, they proposed the use of hemorheological parameters as indicators of endothelial function. Tripolino et al[20] showed the relationship between blood viscosity, carotid artery elasticity, and increased ankle-brachial index. Established cardiovascular risk factors, including hypertension, diabetes mellitus, and elevated BMI, exhibit a correlation with WBV. Toth et al[21] showed the changes in blood rheology parameters in different cardiovascular patient populations. Thus, a close correlation was found between hemorheology and the severity of CAD. These studies showed that the extent of changes in blood rheology is significantly related to the severity of CAD and plays a role in its pathogenesis.[20,21]

The fact that WBV assessment requires different equipment and is difficult to interpret due to its variability has always remained in the background in its relationship with atherosclerosis. In the study conducted by De Simone et al,[7] aiming at the relationship between blood viscosity and cardiovascular risk factors, simple equations that can be used to calculate WBV were shown. In this study, they evaluated the contribution of rheological determinants and reported that HCT was the primary determinant of WBV at varying rates according to shear rates. Most importantly, they produced simple equations to estimate WBV at different shear rates using HCT and total protein levels, with verification by viscometer. Different shear rates are indicators of different hemodynamic environments. High shear rate (HSR) indicates high-velocity blood flow at the peak of systole in large arteries, while LSR reflects low-velocity blood flow at end-diastole. The advantage of De Simone equations is that WBV values in the desired environment can be easily calculated. De Simone formula has been used in different cardiovascular patient populations, including insulin resistance, hypertension, and coronary slow flow phenomenon.[22,23] Tamariz et al[10] showed the close relationship of WBV with insulin resistance in the "Atherosclerosis Risk in Communities Study (ARIC)." It was suggested that these equations provide an adequate estimation of blood viscosity. Based on these studies, De Simone's equation was included in calculating WBV at different shear rates. In this study, the mean age of the restenosis group was 63±10 years, and 78% patients were male. The number of males in the restenosis group was statistically significantly higher compared to the non-restenosis group. However, male gender was not found to be a predictor of ISR in multivariate Cox regression analyses performed at different shear rates. Although several clinical studies have reported a higher risk of ISR for older and male patients compared to female patients, these findings have not been consistent.[24] The fact that the number of males in the ISR group was significantly higher in this study can be explained by the fact that the sample had fewer patients than in other studies and that gender was not distributed homogeneously.

Kaplan–Meier and Cox regression analyses were used to assess WBV's prognostic significance for ISR. Analysis of ISR-free survival curves demonstrated a substantial discrepancy between the groups; increased WBV, irrespective of calculation method (HSR or LSR), correlated significantly with a greater cumulative incidence of ISR. These results corroborate prior research indicating a significant correlation between heightened blood viscosity and endothelial dysfunction, inflammation, and vascular remodeling, collectively contributing to restenosis.[15–18] Increased central blood volume disrupts laminar flow, resulting in elevated turbulent shear stress. This may accelerate neointimal hyperplasia and neo-atherosclerosis, key mechanisms in the pathogenesis of ISR.[13,14,16] Moreover, elevated blood viscosity correlates with augmented leukocyte and platelet adhesion, promoting vascular inflammation and atherogenesis.[18,19]

When the comorbid conditions of the patients in this study were examined, no significant difference was observed between the 2 groups in terms of the incidence of diabetes, hypertension, and dyslipidemia. Diabetes is a risk factor for atherosclerosis as well as for the formation of ISR. The fact that diabetes was not associated with ISR in the study may be because the patients were using antidiabetic drugs and were being followed up for disease regulation. Hypertension is known to be a risk factor for atherosclerosis. Hypertension was shown to be a risk factor for ISR in a study conducted by Singh et al.[25] However, contrary to this study, studies show that hypertension is not associated with ISR.[26] In the study conducted by Wang et al,[27] in which they investigated new predictors in ISR patients with diabetes, it was shown that hypertension and dyslipidemia were not predictors compared to the group without restenosis. Smoking continues to be a risk factor that contributes significantly to cardiovascular morbidity and mortality. However, whether it is a risk factor for developing ISR is controversial. Some studies have shown that it is protective against developing ISR. However, the use of older-generation stents, patient compliance, and the possibility of selecting a population that is more insensitive to smoking were taken into consideration in these studies. A study conducted in the past years by Alexandrescu

et al[28] determined that smoking was associated with ISR. In this study, it was also shown that smoking was an independent predictor for the development of ISR.

One of the most essential steps in developing restenosis is the inflammatory response after stent implantation and the neo-atherosclerosis that occurs afterward. A study determined that CRP levels increased after stent implantation, indicating an inflammatory response. A meta-analysis conducted by Zhu et al[29] showed that high-sensitivity CRP level is a risk for the development of ISR. In this study, CRP level was found to be significantly higher in the restenosis group compared to the group without it, following the literature.

In this study, ISR development was significantly less in patients using statins. This may be attributed to statins' pleiotropic effects and LDL-lowering effect. Walter et al[30] showed that statin nonusers are at higher risk for ISR. It was also found that HDL levels were similar between the 2 groups in this study. A meta-analysis by He et al[31] proved no significant relationship between HDL levels and ISR, similar to this research.

In this study, it was also determined that there was a significant difference between the first implanted stent type (DES or BMS) and the development of ISR in both groups. As is known, although the restenosis risk of DES is lower than BMS, there is still a 5-10% ISR incidence in new-generation DESs.[32] Xu et al[33] determined the stent type as a risk factor associated with ISR and found that ISR was 2.4 times higher in patients implanted with BMS. It was also found that the stent type was an independent predictor of ISR in multivariate regression analyses. It was also shown that the stent length and diameter were independent predictors of ISR. In line with this study, previous studies have demonstrated that the stent length and diameter are associated with ISR.[34,35]

Study Limitations

It is crucial to note that WBV calculation employs an indirect formula instead of viscometric methods. Further strengthening the study's conclusions through viscometric measurements is warranted, despite prior research corroborating the formula. In addition, this study does not include other hemorheological parameters and homocysteine levels that will affect WBV. Another limitation of this study is that the characteristics of the first stent of the patients included in the study, such as balloon inflation time, balloon inflation time, and pre-dilatation – post-dilatation, are unknown.

Coronary artery disease is one of the most common causes of death worldwide. In recent years, stent implantation has become the primary therapeutic procedure for treating a narrowed coronary artery in patients with CAD. Despite advancements, high rates of ISR continue to present a significant clinical problem. This study found that WBV is an independent predictor of ISR development at both LSR and HSR. Therefore, increased blood viscosity may play a role in developing neointimal hyperplasia and ISR due to the endothelial inflammation it causes. This situation may inspire new studies on the pathogenesis of ISR. In addition, simple and inexpensive WBV measurement with the de Simone formula can be applied in routine practice as a parameter to predict the development of ISR before CAG. Further research is required to establish a definitive link between WBV and ISR, necessitating larger, prospective, randomized studies to provide robust evidence and reduce the possibility of confounding variables influencing the findings.

AI Statement: The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work but did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

Data Availability Statement: The data supporting this study's findings are available on request from the corresponding author. Access to the data is restricted due to privacy and ethical considerations.

Ethics Committee Approval: Ethical guidelines for human experimentation, including the 2008 revision of the Helsinki Declaration, and institutional and national review board standards were strictly observed. The institution has granted Ethics Committee Approval (protocol number E1-22-2779; date: July 27, 2022).

Informed Consent: As this was a retrospective study, no informed consent was obtained from the participants.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept – Y.Ç., N.A., M.A.E.; Design – Y.Ç., M.E.; Supervision – M.E., A.N.A.; Data Collection and/or Processing – Y.Ç.; Analysis and/or Interpretation – S.B.; Literature Search – Y.Ç., B.K.; Writing – Y.Ç., A.N.A.; Critical Reviews – M.E., M.A.E.

Disclaimers: The views expressed in this manuscript are solely those of the authors and do not necessarily represent the official policy or position of their respective institutions.

Declaration of Interests: The authors declare that they have no competing interests.

Funding: There is no specific funding related to this research.

REFERENCES

1. Pruthi S, Siddiqui E, Smilowitz NR. Beyond coronary artery disease: assessing the microcirculation. *Rheum Dis Clin North Am*. 2024;50(3):519-533. [CrossRef]
2. Krittanawong C, Rizwan A, Khawaja M, et al. The current state of coronary revascularization: coronary artery bypass graft surgery versus percutaneous coronary interventions. *Curr Cardiol Rep*. 2024;26(9):919-933. [CrossRef]
3. Giacobbe F, Valente E, Morena A, et al. Safety and efficacy of drug-eluting stents for patients at high risk of bleedings: A network meta-analysis. *Catheter Cardiovasc Interv*. 2024;103(6):843-855. [CrossRef]
4. Giacoppo D, Mazzone PM, Capodanno D. Current management of in-stent restenosis. *J Clin Med*. 2024;13(8):2377. [CrossRef]
5. Toprak K, Kaplangoray M, Palice A, et al. Increased whole blood viscosity is associated with primary idiopathic complete atrioventricular block and poor clinical outcomes in these patients. *Clin Hemorheol Microcirc*. 2023;84(2):141-151. [CrossRef]
6. Lee CY, Lee SL, Kim E, et al. Whole blood viscosity reference intervals and its correlation with hematology and serum chemistry in cats using scanning capillary method. *Animals (Basel)*. 2023;13(23):3694. [CrossRef]
7. de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and

physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation*. 1990;81(1):107-117. [CrossRef]
8. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56(23):1897-1907. [CrossRef]
9. Nwose EU, Richards RS. Whole blood viscosity extrapolation formula: note on appropriateness of units. *N Am J Med Sci*. 2011;3(8):384-386. [CrossRef]
10. Tamariz LJ, Young JH, Pankow JS, et al. Blood viscosity and hematocrit as risk factors for type 2 diabetes mellitus: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol*. 2008;168(10):1153-1160. [CrossRef]
11. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med*. 1994;331(8):489-495. [CrossRef]
12. Hao PP, Chen YG, Wang XL, Zhang Y. Efficacy and safety of drug-eluting stents in patients with acute ST-segment-elevation myocardial infarction: a meta-analysis of randomized controlled trials. *Tex Heart Inst J*. 2010;37(5):516-524.
13. Lu ZF, Yin WH, Schoepf UJ, et al. Prediction value of pericoronary fat attenuation index for coronary in-stent restenosis. *Eur Radiol*. 2024;34(8):4950-4959. [CrossRef]
14. Shafiabadi Hassani N, Ogliari LC, Vieira de Oliveira Salerno PR, Pereira GTR, Ribeiro MH, Palma Dallan LA. In-stent restenosis overview: from intravascular imaging to optimal percutaneous coronary intervention management. *Medicina (Kaunas)*. 2024;60(4):549. [CrossRef]
15. Bhak Y, Tenesa A. Mendelian randomization study of whole blood viscosity and cardiovascular diseases. *PLOS One*. 2024;19(4):e0294095. [CrossRef]
16. Dolu K. Whole blood viscosity predicts nondipping circadian pattern in essential hypertension. *Biomark Med*. 2020;14(14):1307-1316. [CrossRef] [published correction appears in *Biomark Med*. 2020 December;14(18):1758. (https://doi.org/10.2217/bmm-2020-0249e1)
17. Gao W, Dong Y, Dong F, et al. Feasibility study of combining wall shear stress and elastography to assess the vascular status of carotid artery. *Curr Med Imaging*. 2024;20:e270323214999. [CrossRef]
18. Valeanu L, Ginghina C, Bubenek-Turconi S. Blood rheology alterations in patients with cardiovascular diseases. *Rom J Anaesth Intensive Care*. 2022;28(2):41-46. [CrossRef]
19. Yagi H, Sumino H, Aoki T, et al. Impaired blood rheology is associated with endothelial dysfunction in patients with coronary risk factors. *Clin Hemorheol Microcirc*. 2016;62(2):139-150. [CrossRef]
20. Tripolino C, Irace C, Carallo C, et al. Association between blood viscosity and common carotid artery elasticity. *Clin Hemorheol Microcirc*. 2016;62(1):55-62. [CrossRef]
21. Toth A, Papp J, Rabai M, et al. The role of hemorheological factors in cardiovascular medicine. *Clin Hemorheol Microcirc*. 2014;56(3):197-204. [CrossRef]
22. Ceyhun G, Birdal O. Relationship between whole blood viscosity and lesion severity in coronary artery disease. *Int J Angiol*. 2021;30(2):117-121. [CrossRef]
23. Cetin MS, Ozcan Cetin EH, Canpolat U, et al. An overlooked parameter in coronary slow flow phenomenon: whole blood viscosity. *Biomark Med*. 2015;9(12):1311-1321. [CrossRef]
24. Brown RA, Williams M, Barker CM, et al. Sex-specific outcomes following revascularization with zotarolimus-eluting stents: comparison of angiographic and late-term clinical results. *Catheter Cardiovasc Interv*. 2010;76(6):804-813. [CrossRef]
25. Singh M, Gersh BJ, McClelland RL, et al. Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial. *Circulation*. 2004;109(22):2727-2731. [CrossRef]
26. Wita K, Kinasz L, Filipecki A, et al. Risk factors of asymptomatic restenosis in patients with first anterior ST elevation myocardial infarction treated by primary percutaneous coronary intervention. *Kardiol Pol*. 2010;68(9):987-993.
27. Wang JL, Qin Z, Wang ZJ, et al. New predictors of in-stent restenosis in patients with diabetes mellitus undergoing percutaneous coronary intervention with drug-eluting stent. *J Geriatr Cardiol*. 2018;15(2):137-145. [CrossRef]
28. Alexandrescu DM, Mitu O, Costache II, et al. Risk factors associated with intra-stent restenosis after percutaneous coronary intervention. *Exp Ther Med*. 2021;22(4):1141. [CrossRef]
29. Zhu X, Chen Y, Xiang L, et al. The long-term prognostic significance of high-sensitive C-reactive protein to in-stent restenosis. *Med (Baltim)*. 2018;97(27):e10679. [CrossRef]
30. Walter DH, Schächinger V, Elsner M, Mach S, Auch-Schwelk W, Zeiher AM. Effect of statin therapy on restenosis after coronary stent implantation. *Am J Cardiol*. 2000;85(8):962-968. [CrossRef]
31. He WJ, Zhou Y, Liu JX, Liu J. Association of baseline high-density lipoprotein levels with restenosis after coronary stenting: a meta-analysis. *Coron Artery Dis*. 2013;24(5):386-391. [CrossRef]
32. Piccolo R, Stefanini GG, Franzone A, et al. Safety and efficacy of resolute zotarolimus-eluting stents compared with everolimus-eluting stents: a meta-analysis. *Circ Cardiovasc Interv*. 2015;8(4):e002223. [CrossRef]
33. Xu B, Li JJ, Yang YJ, et al. A single center investigation of bare-metal or drug-eluting stent restenosis from 1633 consecutive Chinese Han ethnic patients. *Chin Med J (Engl)*. 2006;119(7):533-538. [CrossRef]
34. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;80(4):348-372. [CrossRef]
35. Pelliccia F, Zimarino M, Niccoli G, et al. In-stent restenosis after percutaneous coronary intervention: emerging knowledge on biological pathways. *Eur Heart J Open*. 2023;3(5):oead083. [CrossRef]