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Predictors of no-reflow after coronary stenting in patients with high thrombus burden

Ufuk Yıldırım[1], Metin Çoksevim[1], Abdulkadir Kara[2], Alperen Altınbaş[1], Meliyke Hatun Başer[1]

[1]Department of Cardiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkiye
[2]Department of Cardiology, Samsun Training and Research Hospital, Samsun, Turkiye

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ABSTRACT

Aims: In this study, we aimed to reveal the predictors of no-reflow after coronary stenting in patients with high thrombus burden.

Methods: Patients with acute myocardial infarction who underwent stenting of a coronary lesion with high thrombus burden in the same session between February 2020 and July 2022 in our center were included in this retrospective study. High thrombus burden was accepted as Thrombolysis in Myocardial Infarction (TIMI) grade 4 or 5 thrombus. No-reflow was accepted as TIMI grade ≤2 flow at the end of the procedure. Multivariate logistic regression analysis was executed to ascertain the predictors of no-reflow.

Results: Of the 485 patients included in the study, 407 (83.9%) did not develop no-reflow. Of the 78 (16.1%) patients who developed no-reflow at the end of the procedure, 61 had TIMI 2, 10 had TIMI 1, and 7 had TIMI 0 flow. Age [odds ratio (OR) 1.051; 95% confidence interval (CI) 1.021-1.082; p=.001], accumulated thrombus proximal to the occlusion (OR 3.318; 95% CI 1.176-9.365; p=.023), reference vessel diameter (RVD) greater than 4 mm (OR 2.569; 95% CI 1.005-6.565; p=.049), and TIMI flow grade after wiring or small balloon dilation (OR 0.108; 95% CI 0.065-0.181; p<.001) were the independent predictors of no-reflow.

Conclusion: Older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and the absence of TIMI grade 3 flow after wiring or small balloon dilation may be associated with an increased risk of no-reflow after coronary stenting in patients with high thrombus burden.

Keywords: No-reflow, coronary stenting, high thrombus burden

INTRODUCTION

Despite the considerable advancements in interventional cardiology, coronary lesions with high thrombus burden remain challenging for operators. High thrombus burden may complicate percutaneous coronary intervention (PCI) in several ways, one of which is no-reflow. No-reflow is characterized by inadequate myocardial perfusion despite the relief of mechanical vessel obstruction.[1] This complication may lead to a variety of unfavorable consequences, including arrhythmias, early infarct-associated pericarditis, acute heart failure (HF), adverse cardiac remodeling and chronic HF.[2-5] Predicting the potential for no-reflow, which may even result in mortality, may enable interventional cardiologists to select a more appropriate PCI strategy in order to avoid this complication. In this study, we aimed to reveal the predictors of no-reflow after coronary stenting in patients with high thrombus burden.

METHODS

The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 28.11.2024, Decision No: KAEK 2024/547) and conducted in accordance with the Declaration of Helsinki.

Patients with acute myocardial infarction (MI) who underwent stenting of a coronary lesion with high thrombus burden in the same session between February 2020 and July 2022 in our center were included in this retrospective study. High thrombus burden was accepted as thrombolysis in myocardial infarction (TIMI) grade 4 [thrombus length greater than 2 times the reference vessel diameter (RVD)] or 5 thrombus [totally occluded infarct-related artery (IRA)].[6] Chronic total occlusion as the IRA, intracoronary (IC) fibrinolytic therapy, thrombectomy, and deferred stenting strategy rather than immediate stenting were the exclusion criteria. Two groups were formed as those who developed no-reflow and those who

Corresponding Author: Ufuk Yıldırım, ufukyildirim2715@yahoo.com.tr

did not. No-reflow was accepted as TIMI grade ≤2 flow at the end of the procedure.

The demographic and clinical characteristics of the study population were obtained from the hospital database. Age and gender were recorded. History of hypertension, diabetes, prior MI, prior PCI, and prior coronary artery bypass grafting were noted. Patients exhibiting a glomerular filtration rate of less than 60 ml/min/1.73 m^2 for a minimum of 3 months were deemed to have chronic kidney disease (CKD).[7] Patients on maintenance dialysis were also recorded. The diagnosis at admission and P2Y12 inhibitor choice were noted. Time from first medical contact (FMC) to stenting was documented. FMC was accepted as the patient's arrival time at our hospital.

The procedural characteristics of the study population were assessed by the same interventional cardiologist. IRA and native or in-stent lesion were recorded. Two-dimensional quantitative coronary angiography analysis was used to estimate the diameter stenosis, lesion length, and thrombus length. The RVD was accepted as the diameter reached by the stent or postdilation balloon if used, whichever was higher. The features of high thrombus burden defined by Yip et al.[8] including cutoff occlusion, accumulated thrombus greater than 5 mm proximal to the occlusion, floating thrombus, sustained dye stasis distal to the obstruction, RVD greater than 4 mm, and thrombus length greater than 3 times the RVD were also reviewed. Initial TIMI thrombus grade and initial TIMI flow grade were documented. In patients with an initial lack of antegrade flow, TIMI thrombus grade and TIMI flow grade were reclassified after wiring or small (≤2 mm in diameter) balloon dilation for the purpose of restoring antegrade flow. Predilation, number of stents per lesion, total stent length per lesion, and postdilation were also noted.

Statistical Analysis

The statistical package for social sciences (SPSS) version 25 was used to upload and analyze the research data. The chi-square test was employed to compare categorical variables, which were presented in terms of frequencies and percentages. The Kolmogorov-Smirnov test was implemented to determine the normality of the distribution of continuous variables. An independent samples T test was applied to compare continuous variables with a normal distribution, which were expressed as mean±standard deviation. The Mann-Whitney U test was utilized to compare continuous variables without a normal distribution, which were given as median (minimum-maximum). Multivariate logistic regression analysis was executed to ascertain the predictors of no-reflow, and also TIMI 0 or 1 flow at the end of the procedure. All clinical and procedural characteristics assessed in the study were initially examined through univariate analysis, and variables with p≤0.1 in the univariate analysis were then put under multivariate analysis. p≤0.05 was considered statistically significant.

RESULTS

Of the 485 patients included in the study, 407 (83.9%) did not develop no-reflow. Of the 78 (16.1%) patients who developed no-reflow at the end of the procedure, 61 had TIMI 2, 10 had TIMI 1, and 7 had TIMI 0 flow.

When comparing patients with and without no-reflow (**Table 1**), patients with no-reflow had older age and higher prevalence of CKD (p<.001 and p=.010, respectively). The diameter stenosis, lesion length, and thrombus length were greater in patients with no-reflow (p=.022, p=.002, and p=.021, respectively). Accumulated thrombus proximal to the occlusion was more common in patients with no-reflow (p<.001). Initial TIMI thrombus grade and TIMI thrombus grade after wiring or small balloon dilation were higher (p=.022 and p<.001, respectively), initial TIMI flow grade and TIMI flow grade after wiring or small balloon dilation were lower in patients with no-reflow (p=.050 and p<.001, respectively). The number of stents per lesion and total stent length per lesion were also greater in patients with no-reflow (p=.006 and p=.001, respectively).

Age [odds ratio (OR) 1.051; 95% confidence interval (CI) 1.021-1.082; p=.001], accumulated thrombus proximal to the occlusion (OR 3.318; 95% CI 1.176-9.365; p=.023), RVD greater than 4 mm (OR 2.569; 95% CI 1.005-6.565; p=.049), and TIMI flow grade after wiring or small balloon dilation (OR 0.108; 95% CI 0.065-0.181; p<.001) were the independent predictors of no-reflow (**Table 2**). The only independent predictor of TIMI 0 or 1 flow at the end of the procedure was TIMI flow grade after wiring or small balloon dilation (OR 0.118; 95% CI 0.053-0.262; p<.001) (**Table 3**).

DISCUSSION

In the present study, older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and TIMI flow grade after wiring or small balloon dilation were found to be independently associated with no-reflow after coronary stenting in patients with high thrombus burden. The absence of TIMI grade 3 flow after wiring or small balloon dilation was the only independent predictor of TIMI 0 or 1 flow at the end of the procedure, which could be considered severe no-reflow.

Consistent with the literature, older age was associated with an increased risk of no-reflow in our study.[9-15] Increased number of comorbidities, higher plaque burden, and delayed hospital admission in the elderly may contribute to an increased susceptibility to no-reflow.[13,16] In addition, aging causes progressive endothelial dysfunction and impaired coronary flow reserve, which may act in the pathogenesis of no-reflow.[17]

In our study, high thrombus burden was accepted as TIMI grade 4 or 5 thrombus. However, the features of high thrombus burden defined by Yip et al.[8] were also reviewed in the study. Among these features, accumulated thrombus proximal to the occlusion and RVD greater than 4 mm were found to be independently associated with no-reflow. These features may indicate higher thrombus burden and increased likelihood of distal embolization, which may contribute to the pathogenesis of no-reflow. It is evident that the presence of an IRA with an RVD greater than 4 mm suggests the existence of a substantial thrombus and/or plaque burden. It is also noteworthy that distal embolization of thrombotic remnants typically manifests following stent implantation in large coronary arteries, as opposed to small ones where the thrombus is mostly trapped between the stent and the

Table 1. Clinical and procedural characteristics of patients with and without no-reflow				
Variable		**No-reflow (+) (n=78)**	**No-reflow (-) (n=407)**	**p**
Age (year)		66.0 ± 11.7	60.6 ± 11.4	<.001
Male (%*)		68 (87.2)	336 (82.6)	.316
Hypertension (%*)		37 (47.4)	195 (47.9)	.939
Diabetes (%*)		23 (29.5)	135 (33.2)	.525
Chronic kidney disease (%*)		19 (24.4)	53 (13.0)	.010
Dialysis (%*)		0	3 (0.7)	.447
Prior MI (%*)		12 (15.4)	78 (19.2)	.431
Prior PCI (%*)		10 (12.8)	73 (17.9)	.272
Prior CABG (%*)		3 (3.8)	20 (4.9)	.684
Diagnosis at admission	STEMI (%*)	57 (73.1)	265 (65.1)	.172
	NSTEMI (%*)	21 (26.9)	142 (34.9)	
Time from FMC to stenting (h)		1.0 (0.5-37.0)	1.0 (0.5-74.0)	.519
IRA	LM (%*)	0	2 (0.5)	.324
	LAD (%*)	35 (44.9)	144 (35.4)	
	LCX (%*)	11 (14.1)	88 (21.6)	
	RCA (%*)	29 (37.2)	164 (40.3)	
	SVG (%*)	3 (3.8)	9 (2.2)	
Native/in-stent	Native (%*)	76 (97.4)	391 (96.1)	.558
	In-stent (%*)	2 (2.6)	16 (3.9)	
Diameter stenosis (%)		100 (90-100)	100 (70-100)	.022
P2Y12 inhibitor	Prasugrel (%*)	9 (11.5)	85 (20.9)	.155
	Ticagrelor (%*)	28 (35.9)	136 (33.4)	
	Clopidogrel (%*)	41 (52.6)	186 (45.7)	
RVD (mm)		3.0 (2.3-5.0)	3.0 (2.3-5.0)	.777
Lesion length (mm)		32 (14-84)	26 (8-70)	.002
Thrombus length (mm)		8 (0-30)	5 (0-42)	.021
Cutoff occlusion (%*)		8 (10.3)	22 (5.4)	.103
Accumulated thrombus proximal to the occlusion (%*)		16 (20.5)	22 (5.4)	<.001
Floating thrombus (%*)		0	6 (1.5)	.281
Sustained dye stasis distal to the obstruction (%*)		6 (7.7)	45 (11.1)	.375
RVD greater than 4 mm (%*)		13 (16.7)	38 (9.3)	.053
Thrombus length greater than 3 times RVD (%*)		3 (3.8)	30 (7.4)	.257
Initial TIMI thrombus grade	4 (%*)	7 (9.0)	81 (19.9)	.022
	5 (%*)	71 (91.0)	326 (80.1)	
TIMI thrombus grade after wiring or small balloon dilation	0 (%*)	11 (14.1)	71 (17.4)	<.001
	1 (%*)	11 (14.1)	78 (19.2)	
	2 (%*)	1 (1.3)	14 (3.4)	
	3 (%*)	12 (15.4)	80 (19.7)	
	4 (%*)	36 (46.2)	161 (39.6)	
	5 (%*)	7 (9.0)	3 (0.7)	
Initial TIMI flow grade	0 (%*)	71 (91.0)	320 (78.6)	.050
	1 (%*)	0	6 (1.5)	
	2 (%*)	4 (5.1)	25 (6.1)	
	3 (%*)	3 (3.8)	56 (13.8)	
TIMI flow grade after wiring or small balloon dilation	0 (%*)	3 (3.8)	0	<.001
	1 (%*)	17 (21.8)	11 (2.7)	
	2 (%*)	44 (56.4)	66 (16.2)	
	3 (%*)	14 (17.9)	330 (81.1)	
Predilation (%*)		72 (92.3)	363 (89.2)	.407
Number of stents per lesion		1.3 ± 0.5	1.1 ± 0.4	.006
Total stent length per lesion (mm)		38 (16-96)	32 (15-96)	.001
Postdilation (%*)		35 (44.9)	206 (50.6)	.353

*Column percentage, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction, FMC: First medical contact, IRA: Infarct-related artery, LM: Left main coronary artery, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, SVG: Saphenous vein graft, RVD: Reference vessel diameter, TIMI: Thrombolysis in Myocardial Infarction

Table 2. Predictors of no-reflow in multivariate logistic regression analysis

Variable	OR (95% CI)	p
Age	1.051 (1.021-1.082)	.001
Chronic kidney disease	1.664 (0.742-3.733)	.217
Lesion length	1.032 (0.992-1.073)	.118
Thrombus length	0.972 (0.915-1.034)	.371
Accumulated thrombus proximal to the occlusion	3.318 (1.176-9.365)	.023
RVD greater than 4 mm	2.569 (1.005-6.565)	.049
Initial TIMI thrombus grade	1.553 (0.553-4.362)	.404
TIMI thrombus grade after wiring or small balloon dilation	0.921 (0.696-1.218)	.563
TIMI flow grade after wiring or small balloon dilation	0.108 (0.065-0.181)	<.001
Number of stents per lesion	0.553 (0.193-1.587)	.271

OR: Odds ratio, CI: Confidence interval, RVD: Reference vessel diameter, TIMI: Thrombolysis in myocardial infarction

Table 3. Predictors of TIMI 0 or 1 flow in multivariate logistic regression analysis

Variable	OR (95% CI)	p
Chronic kidney disease	2.507 (0.700-8.976)	.158
Accumulated thrombus proximal to the occlusion	1.267 (0.265-6.060)	.767
RVD greater than 4 mm	2.515 (0.607-10.420)	.204
TIMI thrombus grade after wiring or small balloon dilation	0.920 (0.620-1.366)	.679
TIMI flow grade after wiring or small balloon dilation	0.118 (0.053-0.262)	<.001
Number of stents per lesion	0.874 (0.261-2.929)	.827

OR: Odds ratio, CI: Confidence interval, RVD: Reference vessel diameter, TIMI: Thrombolysis in myocardial infarction

vessel wall. Furthermore, an IRA with a larger RVD may be associated with larger infarct size and greater extent of ischemia, which may also contribute to the pathogenesis of no-reflow.[18]

Initial TIMI thrombus grade and initial TIMI flow grade are inadequate for predicting the occurrence of no-reflow after coronary stenting. Therefore, we also evaluated TIMI thrombus grade and TIMI flow grade after wiring or small (≤2 mm in diameter) balloon dilation in the present study. Multivariate logistic regression analyses demonstrated that TIMI flow grade after wiring or small balloon dilation was an independent predictor of no-reflow, as well as TIMI 0 or 1 flow at the end of the procedure. This finding may be suggestive of potential clinical implications. In patients with the absence of TIMI grade 3 flow after wiring or small balloon dilation, deferred stenting may be reasonable in selected cases. This is particularly applicable for patients with TIMI grade 2 flow after wiring or small balloon dilation, in the absence of ongoing ischemic symptoms. Antithrombotic management with repeat coronary angiography in 48 hours may be considered for these patients.[19] TIMI 0 or 1 flow after wiring or small balloon dilation represents a much more challenging scenario in patients with high thrombus burden. IC administration of fibrinolytic agents and glycoprotein (GP) IIb/IIIa inhibitors, thrombectomy, or deferred stenting in the absence of ongoing ischemia may be viable options. However, the optimal management strategy remains unclear in these patients.

Diabetes has been associated with impaired microvascular reperfusion in patients undergoing primary PCI.[20] However, a review of the extant literature reveals conflicting results regarding the impact of diabetes on the development of no-reflow. While certain clinical studies have identified diabetes as an independent predictor of no-reflow after PCI,[10,21] contradictory findings have also been reported in other studies.[8,11-15] In the present study, the prevalence of diabetes was found to be similar in patients with and without no-reflow. The observed inconsistency among clinical studies in this regard may be related to variations in patient enrollment criteria and the definition of no-reflow.

Limitations

Our study had several limitations. It was a retrospective, single-center study with a relatively small sample size. We did not have data on time from symptom onset to stenting, Killip class, left ventricular ejection fraction and troponin level at admission, as well as pre-PCI GP IIb/IIIa inhibitor use. Data regarding the management of no-reflow were also missing. Coronary artery flow was assessed visually using the TIMI flow grade, which is limited by interobserver variability and the need for a more objective quantification of the different degrees of complete perfusion in a coronary artery. Finally, myocardial blush grade was not incorporated into the definition of no-reflow, as the majority of angiographic movies were not sufficiently long to visualize the myocardial blush.

CONCLUSION

Older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and the absence of TIMI grade 3 flow after wiring or small balloon dilation may be associated with an increased risk of no-reflow after coronary stenting in patients with high thrombus burden.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 28.11.2024, Decision No: KAEK 2024/547).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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