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Association Between Atherogenic Index of Plasma and Atherogenic Coefficient and in-Stent Restenosis After Drug-eluting Stent Implantation for Stable Coronary Artery Disease

Yasin Yüksel[1], Cennet Yıldız[2], Burak Ayça[3], Fahrettin Katkat[4], Süleyman Çağan Efe[5], Dilay Karabulut[2], Fatma Nihan Turhan Çağlar[2]

[1]Private Reyap Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[4]Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[5]University of Health Sciences Turkey, İstanbul Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: Despite improvements in stent science, in-stent restenosis (ISR) remains a major problem. This study was designed to evaluate the atherogenic index of plasma (AIP) and atherogenic coefficient (AC) levels and their predictive values in patients who developed ISR after drug-eluting stent implantation for stable coronary artery disease.

Methods: One hundred ninety-nine patients with ISR and 377 without ISR were included in the study. The biochemical and hematological parameters of the patients were measured. The AIP and AC values were calculated.

Results: Patients with ISR had significantly longer stent length, lower stent diameter, lower ejection fraction, and higher SYNTAX score. They also had significantly higher levels of low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol, AIP, and AC compared to that of patients who did not develop ISR. AIP had a sensitivity of 61.3% and specificity of 72.1% for predicting ISR a cut-off value of 0.58. AC had sensitivity and specificity of 69.8% and 58.8%, respectively, for the presence of ISR a cut-off value of 3.44. LDL-C level of 111.5 mg/dL had sensitivity and specificity of 65.3% and 54% for developing ISR, respectively. Paired comparisons of area difference under the receiver operating characteristic curve showed that AIP and AC had significantly greater area compared with that of LDL-C. Stent diameter, stent length, SYNTAX score, ejection fraction, AIP, and AC were the predictors of ISR.

Conclusion: AIP and AC had higher specificities compared with that of LDL-C in predicting ISR. The calculation of AIP and AC is simple and could be used easily in clinical practice.

Keywords: Atherogenic index of plasma, atherogenic coefficient, in-stent restenosis

Introduction

The treatment of coronary artery disease (CAD) with stent implantation has become a standard procedure in clinical practice. Although the stent implantation success rate is high, stent thrombosis and in-stent restenosis (ISR) continue to be problematic. ISR, which is defined as more than a 50% reduction in stent luminal diameter, occurs within one year after stent implantation in approximately 30% and 10% of patients who undergo bare metal stent (BMS) and drug-eluting stent (DES) implantation, respectively (1). Neointimal hyperplasia with infiltration of inflammatory cells into the stent area and development of neoatherosclerosis have been proposed as major contributory mechanisms in the development of ISR (2). Stent related factors, including stent length, diameter, and position; patient-related factors, including diabetes mellitus (DM), hypertension (HT), higher hs-C-reactive protein, low-density lipoprotein-cholesterol (LDL-C), and homocysteine levels; and lesion-related factors, including bifurcation lesions, have been found as independent predictors of ISR (3,4).

The atherogenic index of plasma (AIP) and atherogenic coefficient (AC), two biomarkers that are calculated from blood lipid parameters, could provide more robust information compared to single lipid parameter measurement. AC, which is calculated by dividing non-high-density lipoprotein-cholesterol (non-HDL-C) to HDL-C levels, more closely reflects apolipoprotein B levels, which is a superior measure of atherogenic risk than LDL-C levels (5). Similarly, AIP, which is derived from the logarithmic transformation of the triglyceride (TG) to HDL-C ratio, has been suggested to provide information about the equilibrium between atherogenic and

Address for Correspondence: Cennet Yıldız MD, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 533 746 99 96 **E-mail:** cennet_yildiz@live.com **ORCID ID:** orcid.org/0000-0003-2456-3206

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antiatherogenic factors (6). Several studies have shown that AIP and AC associated with the existence of DM, metabolic syndrome, CAD, and obesity are strongly correlated with oxidative stress (5,7-11). In this study, the AIP and AC values of patients with ISR after receiving a DES were evaluated and compared with those of the controls. We investigated whether AIP and AC had any value in predicting ISR development after DES implantation.

Methods

We retrospectively screened coronary angiography files of 6,358 patients who underwent coronary angiography between August 2016 and February 2022 in a cardiology clinic of a tertiary hospital center. The clinical and demographic characteristics of the patients were picked from the data system. Patients who were older than eighteen years of age and who had stents implanted for stable CAD were included in the study. Patients with inflammatory, hematological, infectious diseases, thyroid function abnormalities, hepatic and/or renal failure, acute coronary syndrome, and BMS implantation, had stents implanted at bypass graft lesions were excluded. Patients who underwent DES implantation and developed ISR was enrolled in the study. For this purpose, angiographic examinations of the patients who underwent DES implantation for stable CAD were reevaluated. The mean follow-up period between percutaneous intervention and coronary angiography was 6 to 24 months with a median of 11 months. The indications of coronary angiography were stable angina pectoris or the presence of myocardial ischemia on exercise stress test or myocardial perfusion imaging. During the study period, 717 patients underwent repeat coronary angiography after percutaneous intervention. Of these patients, 108 of them underwent coronary angiography with the diagnosis of acute coronary syndrome, 13 of them had stent implantation in venous bypass grafts, 28 of them had bare-metal stent implantation, and 13 patients had severe renal, hepatic, inflammatory, or oncologic diseases and were excluded from the study. The remaining 536 patients constituted our study population. A total of 199 patients who developed ISR and 337 patients who did not develop ISR were included as study and control groups, respectively. During the study period, ten operators performed percutaneous coronary interventions. The approval of the study was obtained from a University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 238, date: 22.07.2022) and it was conducted in concordance with the declaration of Helsinki. Informed consent of all patients was also obtained before study inclusion.

Patients were required to be in an overnight fasting state before blood sample collection. All blood samples were taken from the forearm vein in a sitting position. The biochemical and hematological parameters of the patients were measured. AIP was determined from the logarithmic transformation of the TG to HDL-C ratio. AC was computed from the division of non-HDL-C to HDL-C. A patient was considered a diabetic if she/he had blood glucose levels of greater than 125 mg/dL or was taking anti-diabetic drugs. HT was interpreted as systolic and/or diastolic blood pressures greater than 140 and 90 mmHg or taking anti-hypertensive drugs. Dyslipidemia was interpreted as blood levels of total cholesterol (TC) and LDL-C levels of greater than 200 mg/dL and 100 mg/dL, respectively.

The Siemens Axiom Artis Zee Cath Lab system was used for the coronary angiographic evaluations of the patients. Coronary angiography was performed from common femoral arterial access and 6F catheter was inserted into the arterial system with the Judkins technique. Images of coronary arteries from different imaging planes were obtained. The indication for coronary angiography was the presence of patients' symptoms, ischemia on an exercise stress test, or myocardial perfusion scanning findings. ISR was defined as more than 50% reduction in the luminal diameter within the stent or within 5 mm distal or proximal to the stented region. The SYNTAX score for each patient was calculated using an online calculator.

Statistical Analysis

Distribution of the data was assessed by evaluating skewness, kurtosis of the data, and by use of Kolmogorow-Smirnow test. Comparisons of the patients who had ISR and did not have ISR were performed by using the Mann-Whitney U test or Independent samples-t test for the non-normally and normally distributed data, respectively. Receiver operating characteristic (ROC) curve analysis was used to check out the values of AIP and AC for prediction of ISR. Univariate logistic analysis was conducted to determine the predictors for the presence of ISR. Parameters that were found to be meaningful in univariate analysis were put into multivariate logistic regression analysis. A two-tailed p value of less than 0.05 was considered significant.

Results

The mean ages of the study and control groups were 63.20±10.96 years and 63.07±10.53 years, respectively. We did not find any differences between the two groups with respect to age, gender, body mass index, smoking habits, the presence of DM, HT, hyperlipidemia, creatinine, albumin, hemoglobin levels, and neutrophil, lymphocyte, monocyte, and platelet counts. The ISR patients had significantly longer stent lengths, lower stent diameters, lower ejection fractions, and higher SYNTAX scores. They also had significantly higher levels of LDL-C, TG, non-HDL-C, TC, AIP, and AC compared with those of patients without ISR. Statin use was lower the study group compared in the control group. the clinical and biochemical variables of the two groups are presented in Table 1.

According to the ROC curve analysis, AIP had a sensitivity of 61.3% and a specificity of 72.1% for predicting ISR, with a cut-off value of 0.58. It was found that AC had sensitivity and specificity of 69.8% and 58.8%, respectively, for the presence of ISR with a cut-off value of 3.44. LDL-C level of 111.5 mg/dL had sensitivity and specificity of 65.3% and 54% for developing ISR, respectively. Table 2 and Figure 1 show the ROC curve results of for AIP and AC. Paired comparisons of area difference under the ROC curve showed that AIP and AC had significantly greater area compared with that of LDL-C (Table 3).

Univariate logistic regression analysis demonstrated that stent diameter, stent length, SYNTAX score, ejection fraction, TC, HDL-C, TG, LDL-C, AIP, and AC were independent predictors of the presence of ISR.

Table 1. Clinical and biochemical variables of the two groups

	Control group restenosis (-) (n=337)	Study group restenosis (+) (n=199)	p
Age (years)	63.07±10.53	63.20±10.96	0.896
Gender (n, %)			0.343
Male	252 (74.8)	156 (78.4)	-
Female	85 (25.2)	43 (21.6)	-
Smoking (n, %)			0.867
No smoking	156 (46.3)	89 (16.6)	-
Current smoking	126 (37.4)	79 (39.7)	-
Ex smoker	55 (16.3)	31 (5.7)	-
Diabetes mellitus (n, %)	119 (35.3)	76 (38.2)	0.503
Hypertension (n, %)	307 (91.1)	185 (93.0)	0.447
Hyperlipidemia (n, %)	314 (93.2)	176 (88.4)	0.059
Stent diameter (mm)	3.0 (2.75-3.25)	2.75 (2.75-3.0)	**<0.001**
Stent length (mm)	20 (20-24)	24 (20-28)	**<0.001**
BMI (kg/m^2)	27.68 (25.30-30.10)	27.60 (25.30-29.39)	0.551
Syntax score	8 (5-13.75)	12 (7-18)	**<0.001**
Ejection fraction (%)	56.11±7.72	52.92±9.85	**<0.001**
Creatinine (mg/dL)	0.88 (0.71-1.06)	0.86 (0.72-1.06)	0.750
GFR (mL/min/1.73 m^2)	88 (70-101)	89 (69-103)	0.896
TC (mg/dL)	180 (147.7-218.8)	198.8 (156-237)	**0.003**
LDL-C (mg/dL)	109 (88.5-136.5)	125 (87-155)	**0.005**
Triglycerides (mg/dL)	126 (96.5-169.59	166 (124-217)	**<0.001**
HDL-C (mg/dL)	42 (36-48.5)	39 (34-44)	**<0.001**
Non-HDL-C	135.2 (107.2-173.2)	160 (118-196.8)	**<0.001**
Atherogenic index of plasma	0.46 (0.33-0.61)	0.64 (0.47-0.77)	**<0.001**
Atherogenic coefficient	3.22 (2.5-4.12)	4.15 (3.18-4.97)	**<0.001**
Albumin (g/L)	4.1 (3.8-4.31)	4.12 (3.82-4.4)	**0.030**
Hemoglobin (g/dL)	13.2 (11.5-14.4)	13.3 (11.8-14.5)	0.288
Neutrophil (10^9/L)	5.51 (4.18-7.12)	5.12 (4.11-6.73)	0.314
Platelets (10^9/L) (10^9/L)	243 (197-287)	237 (195-291)	0.837
Lymphocytes (10^9/L)	2.09 (1.66-2.59)	2.18 (1.51-2.74)	0.639
Monocytes (10^9/L)	0.69 (0.51-0.81)	0.69 (0.54-0.85)	0.319
ACEI/ARB (n, %)	260 (77.2)	157 (78.9)	0.639
B-blocker (n, %)	292 (86.6)	177 (88.9)	0.437
Ca-channel blocker (n, %)	110 (32.8)	59 (29.6)	0.471
Diuretic (n, %)	122 (36.2)	76 (38.2)	0.645
Statin (n, %)	262 (77.7)	133 (66.8)	**0.006**
ASA (n, %)	296 (87.8)	163 (81.9)	0.059
Clopidogrel (n, %)	174 (51.6)	124 (62.3)	**0.018**
Oral anticoagulant (n, %)	44 (13.1)	30 (15.1)	0.513
Anti-diabetic (n, %)			0.338
Oral antidiabetic	91 (27)	52 (26.1)	-
Insulin	29 (8.6)	25 (12.6)	-
COPD	51 (15.1)	30 (15.1)	0.986

BMI: Body mass index, GFR: Glomerular filtration rate, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, COPD: Chronic obstructive pulmonary disease

Table 2. ROC curve results of AIP and AC for prediction of ISR

	AUC	p	95% CI	Cut-off	Sensitivity	Specificity
LDL-C	0.573	0.005	0.522-0.625	111.5	65.3	54.0
AIP	0.672	<0.001	0.623-0.720	0.58	61.3	72.1
AC	0.670	<0.001	0.622-0.718	3.44	69.8	58.8

ROC: Receiver operating characteristic, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient, AUC: Area under the curve, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol

Table 3. Paired comparisons of area difference under the ROC curve

	z	p	AUC difference	95% CI
LDL-C/AIP	-2.809	0.005	-0.098	-0.167- -0.030
LDL-C/AC	-4.768	<0.001	-0.097	-0.137- -0.057
AIP/AC	0.069	0.945	0.002	-0.043-0.046

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient

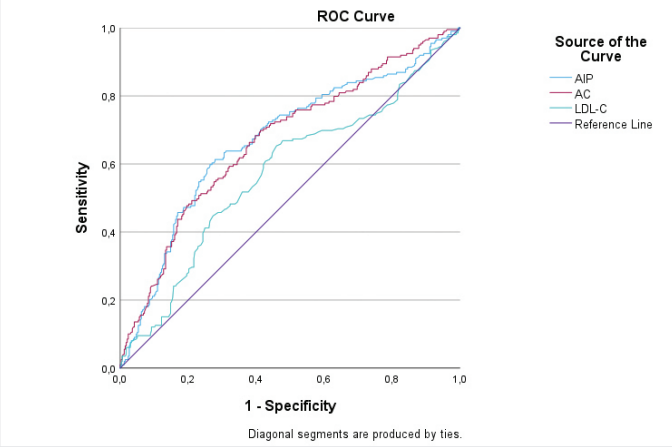

Figure 1. ROC curves of AIP, AC, and LDL-C for prediction of ISR

ROC: Receiver operating characteristic, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient, LDL-C: Low-density lipoprotein cholesterol, ISR: In-stent restenosis

Variables that were found to have meaningful results were put into multivariate logistic regression analysis. We conducted two models of multivariate logistic regression analysis. In the first model, AIP and AC were included in the analysis. According to the results of multivariate analysis, stent diameter, stent length, SYNTAX score, ejection fraction, AIP, and AC were the predictors of ISR. In the second model, TG, HDL-C, and LDL-C were included in the analysis. The results of the second model demonstrated that stent diameter, stent length, SYNTAX score, ejection fraction, LDL-C, TG, and HDL-C were the predictors of ISR. AIP had the greatest odds ratio with a value of 3.979. Table 4, 5 show the results of the univariate and multivariate logistic regression analyses results, respectively.

Discussion

Our study revealed that in addition to the risk factors of stent length, stent diameter, SYNTAX score, ejection fraction, and lipid parameters, including LDL-C, HDL-C, and TG, both AIP and AC had a statistically significant value for predicting ISR. A comparison of the ROC curves demonstrated that AIP and AC each had a significantly higher area under the curve compared to LDL-C. Additionally, among the lipid parameters, AIP had the highest odds ratio for predicting ISR.

Although the incidence of ISR with DES is lower than that associated with BMS, ISR remains a therapeutic challenge (12). Several studies have investigated the risk factors for ISR, with most of finding that cytokines and biomarkers, such as C-reactive protein, homocysteine, and tumor necrosis factor-α, are associated with the presence of ISR (13-15). Additionally, patient-related and lesion-related risk factors have been assessed in various studies, which have found that stent length, diameter, bifurcation lesions, and the presence of DM and HT are risk factors for ISR (3).

Hyperlipidemia is a major factor related to the development of atherosclerosis. Increased levels of LDL-C stimulate inflammation, and cause endothelial damage and cholesterol collection in the vessel wall (16). However, the role of hyperlipidemia in the occurrence of ISR remains less clear, and studies investigating the relationship between hyperlipidemia and ISR have yielded weaker associations. In Kim et al.'s (17) study, patients with a small LDL-C particle size had higher rates of ISR, even after controlling for other CAD risk factors. Fang et al. (18) assessed the LDL-C to HDL-C ratio in acute coronary syndrome patients treated with percutaneous intervention and found that the ratio had a good predictive performance for the presence of ISR. Investigated the risk factors for ISR in patients treated for chronic coronary syndromes. Although TC, HDL-C, and TG levels did not differ between patients with or without ISR, LDL-C levels were significantly elevated in ISR patients (4). Özkalaycı et al. (19) showed that the TG glucose index, a surrogate marker of insulin resistance, had a better value compared the TG/HDL-C ratio and glucose levels in predicting all-cause mortality in ST-elevation myocardial infarction patients. The value of the TG glucose index in risk stratification and prediction of adverse events in patients with ST-elevation myocardial infarction has also been shown in other studies (20). However, Xu et al. (21) did not find any association between lipid parameters and the development of ISR. Similarly, Li et al. (2) found no differences in the lipid profile of patients with or without ISR. Our results were align with the previous studies that found abnormalities in lipid parameters to be a risk factor for ISR.

Table 4. Univariate logistic regression for the presence of in-stent restenosis

	p	OR	95% CI
Age	0.896	1.001	0.985-1.018
Stent diameter	<0.001	0.059	0.026-0.131
Stent length	<0.001	1.325	1.248-1.408
BMI	0.164	0.969	0.927-1.013
Smoking	0.899	1.016	0.798-1.292
Syntax score	<0.001	1.058	1.033-1.083
Ejection fraction	<0.001	0.959	0.940-0.979
Creatinine	0.449	1.098	0.862-1.399
GFR	0.876	0.999	0.993-1.006
TC	0.002	1.005	1.002-1.009
LDL-C	0.006	1.006	1.002-1.010
Triglyceride	<0.001	1.005	1.003-1.008
HDL-C	<0.001	0.995	0.935-0.976
Atherogenic index of plasma	<0.001	11.253	5.004-25.305
Atherogenic coefficient	<0.001	1.613	1.393-1.869
Albumin	0.052	1.529	0.997-2.344
Hemoglobin	0.198	1.060	0.970-1.158
Neutrophil	0.456	0.969	0.892-1.053
Platelet	0.803	1.000	0.998-1.002
Lymphocyte	0.359	1.100	0.897-1.348
Monocyte	0.542	1.252	0608-2.570
Diabetes mellitus	0.503	1.132	0.787-1.627
Hypertension	0.448	1.291	0.667-2.499

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, GFR: Glomerular filtration rate, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

Table 5. Multivariate logistic regression for the presence of in-stent restenosis

Model A

	p	OR	95% CI
Stent diameter	<0.001	0.053	0.020-0.141
Stent length	<0.001	1.348	1.258-1.446
Syntax score	0.002	1.047	1.017-1.078
Ejection fraction	<0.001	0.953	0.929-0.978
Atherogenic index of plasma	0.022	3.979	1.218-12.997
Atherogenic coefficient	0.036	1.270	1.016-1.586

OR: Odds ratio, CI: Confidence interval

Model B

	p	OR	95% CI
Stent diameter	<0.001	0.050	0.019-0.132
Stent length	<0.001	1.345	1.255-1.442
Syntax score	0.002	1.048	1.018-1.079
Ejection fraction	<0.001	0.954	0.930-0.978
LDL-C	0.043	1.006	1.000-1.011
Triglyceride	0.003	1.004	1.001-1.007
HDL-C	0.039	0.971	0.945-0.999

OR: Odds ratio, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

The pathogenesis of ISR has not been fully elucidated and involves complex pathological processes. Vascular wall injury and endothelial denudation caused by balloon dilatation and stent implantation result in an inflammatory response characterized by vascular smooth muscle cell migration, proliferation, extracellular matrix synthesis, and neointimal proliferation (22). Incomplete regeneration of the endothelium leads to excessive uptake of lipids from circulation and foam cell formation, which contributes to the occurrence of neoatherogenesis (23). Neoatherosclerosis, which is characterized by impaired endothelial healing with lipoprotein migration into the subendothelium, results in late stent failure, including ISR and thrombosis (24,25). As such, inflammation and atherosclerotic progression are probably the two main mechanisms for the occurrence of ISR. Consistent with these findings, we found that increased levels of TC, LDL-C, and TG and decreased levels of HDL-C predicted ISR. According to the ROC curve analysis, both AIP and AC had higher specificities compared to LDL-C in predicting ISR. Moreover, among the lipid parameters, AIP had the highest odds ratio in predicting ISR.

Study Limitations

This was a single -center study and had a retrospective design. We did not use intravascular ultrasound or optical coherence tomography for evaluating ISR. Our study could fail to show all confounding risk factors for ISR and fails to evaluate the effect of consecutive changes in AIP during follow-up on ISR incidence. Finally, operator experience might have affected the outcomes.

Conclusion

Development of ISR necessitates repeat interventions that hamper the quality of life of the patients and are associated with increased mortality. As such, secondary prophylaxis with the aim of prevention of ISR is critical after percutaneous interventions. Both AIP and AC had higher specificities compared with that of LDL-C in predicting ISR. The calculation of these parameters is simple and could be used easily in clinical practice. To confirm our findings, multicenter, randomized, and prospective studies are necessary.

Ethics Committee Approval: The approval of the study was obtained from a University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 238, date: 22.07.2022) and it was conducted in concordance with the declaration of Helsinki.

Informed Consent: Informed consent of all patients was also obtained before study inclusion.

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