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Original Research

A Novel Score for an Old Enemy: Atherogenic Plasma Index Predicts In-Stent Restenosis among Stable Angina Pectoris Patients

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Abstract

Objectives: Although the association of Atherogenic index of plasma (AIP) with coronary artery disease (CAD) and atherosclerosis is known, the relationship between AIP and in-stent restenosis (ISR) remains unclear. We aimed to investigate the relationship between AIP and ISR in patients with stable angina pectoris (SAP) treated with drug-eluting stent (DES).

Methods: Patients with a history of DES implantation following stable angina were evaluated between January 2015 and November 2019 in this observational and retrospective study. 608 eligible patients were dichotomized into ISR+ (n=241) and ISR- (n=367). ISR was defined as the presence of 50% or greater stenosis. AIP was defined as log [TG/HDL-C].

Results: AIP levels were significantly higher in patients who developed ISR compared with those who did not (0.33 [0.15-0.52] vs 0.06 [-0.08-0.21] respectively, p<0.001). The AUC value of AIP levels for predicting ISR was 0.746 (p<0.001). Multivariate logistic regression analysis revealed that AIP, diabetes mellitus, higher LDL-C levels and lower LVEF values were independently associated with ISR.

Conclusion: Multivariate analysis revealed that AIP was strongly independently associated with ISR. Using this novel inexpensive and easily calculable index may provide early recognition of ISR in patients with SAP who were treated with DES.

Keywords: Atherogenic index of plasma, drug eluting stent, in stent restenosis, stable angina pectoris

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In-stent restenosis (ISR) is defined as 50% or more narrowing of the stented segment of the coronary arteries. It commonly occurs within the first 12 months after stent implantation.[1] Despite advances in stent design, drug and polymer structure in modern DESs; the incidence of ISR varies between 5% and 10%, and therefore it remains an important clinical problem.[2,3]

The predisposing factors and pathogenesis of DES-ISR remain unclear.[4] Predisposing factors are grouped under three main headings in relation to lesion, procedure and patient. Small vessel diameter, stent implantation in saphenous graft, osteal, long, and calcific lesions are the most common lesion-related factors. The most important patient-related risk factors are hypertension, diabetes and hyperlipidemia.[5,6]

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A high plasma level of low-density cholesterol (LDL-C) is an independent risk factor for CAD, and one of main goals in the treatment of CAD.[7,8] Several studies have shown that small-dense LDL-C (sdLDL-C) is more atherogenic than total LDL-C.[9] The Atherogenic index of plasma (AIP) is calculated by the logarithm of the molar ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) level. AIP is associated with LDL-C particles and fractional esterification of cholesterol.[10] AIP reflects the level of atherogenic sdLDL-C and rapid progression of coronary atherosclerosis. This value has been applied as an index for CAD.[11]

Although the association of AIP with CAD and atherosclerosis is well documented in many studies, the relationship between AIP and ISR remains unclear. Therefore, we aimed to investigate the relationship between AIP and ISR in patients with stable angina pectoris (SAP) treated with DES.

Methods

Patients referred for coronary angiography for stable angina pectoris and with a history of DES implantation were evaluated between January 2015 and November 2019 in this observational and retrospectively designed study. Exclusion criteria were as follows: a history of inflammatory disease, severe kidney or liver disease, coronary artery bypass grafting operation and malignancy. There were 680 patients who had coronary angiography for stable angina pectoris and with a history of DES implantation, and 608 patients were found to be eligible according to exclusion criteria and included in the study. Among 608 eligible patients, those who had a re-indication for coronary angiography (CA) due to angina symptoms or abnormal stress test results during follow-up created the study cohort for final analysis.

Study population was dichotomized into ISR+ (n=241) and ISR- (n=367) according to the presence of ISR. ISR was defined as the presence of 50% or greater stenosis of a previously implanted stent in at least one of the three main coronary arteries (left anterior descending, left circumflex, or right coronary artery) or major branches, and was assessed by two independent, experienced interventional cardiologists who were blinded to the study design. A third experienced interventional cardiologist evaluated the angiographic findings in case of a discrepancy between the two.

We compared the following clinical features among the groups: demographical information, medical history including diabetes mellitus, hypertension, prior myocardial infarction, prior cerebrovascular disease, left ventricular ejection fraction, regularly used drugs including aspirin, statins, beta-blockers, renin-angiotensin-aldosterone system inhibitors, oral antidiabetic drugs and insulin. We also compared the following biochemical and hematological parameters among the groups: glucose, hemoglobin, white blood cell, lymphocyte, neutrophil, platelet, mean platelet volume, glomerular filtration rate at admission, creatinine, thyroid stimulating hormone, hemoglobin A1c, total cholesterol, LDL-C, HDL-C, TG, AIP. In addition, baseline angiographic characteristics were compared. The time between two CAGs was also calculated for all patients.

Experienced operators using standard techniques as defined by the guidelines performed each CA. The decision for choosing femoral or radial route was dependent on operators' discretion.

Each patient was evaluated by transthoracic echocardiography within the 24 hours following CA (Vivid 3, GE Medical System, Norway). Simpson's method was used for measurement of left ventricular ejection fraction (LVEF), according to the recommendations of the American Society of Echocardiography.

Blood samples were taken after 10 to 12 hours of fasting at the time of hospital admission for CA and centrifuged at 850 g for 10 µmin. Serum levels of the fasting lipid panel including total cholesterol, TG, LDL-C, and HDL-C; also, hemogram parameters, thyroid function tests, hemoglobin A1c, creatinine, glucose and uric acid levels were measured using standard laboratory techniques. Diabetes mellitus was determined as fasting blood glucose value >126 mg/dl or HbA1c value >6.5% or a history of antidiabetic drug use, eGFR of the patients was calculated with the Levey-modified Modification of Diet in Renal Disease formula: (186.3 × serum creatinine [mg/dL]−1.154) × (age [years]−0.203) × (0.742 if female).

The use of antihypertensive medications and a history of hypertension led to the diagnosis of hypertension. Hyperlipidemia was defined as cholesterol-lowering drug use, LDL-C levels exceeding 140 mg/dl, or TG levels exceeding 150 mg/dl. In order to diagnose chronic kidney disease (CKD), an estimated eGFR value of <60 mg/dl was required. AIP was defined as the logarithm of (TG/HDL-C).

Ethics committee approval was obtained from the Clinical Research Ethics Committee (Ethics Committee Number: 3478 Date: 22.03.2022). This study was conducted according to the declaration of Helsinki Informed consent was obtained from each participant. Those who did not volunteer to participate in the study or did not give their consent were excluded from the study.

Statistical Analysis

The statistical analysis was conducted using SPSS 22 (SPSS Inc., Chicago, IL, U.S.A.). Using the Kolmogorov-Smirnov test, the distribution of data was analyzed. All the information was presented as the median and interquartile range (IQR). The documentation of categorical variables included numbers and percentages. Continuous variables were compared between two groups using the t-test or Mann-Whitney, as applicable, for independent samples. We compared categorical data using the chi-square or Fisher exact test. To evaluate the effect of AIP on ISR, we developed a logistic regression model that included AIP, age, Diabetes mellitus (DM), LDL-C, history of prior myocardial infarction, LVEF, and duration between the two CAGs. Covariates that were found to be significant in the univariate analysis ($p<0.10$) or that were believed to have clinical significance were incorporated into the multivariate model during its construction. Analysis of the receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of AIP for ISR. $p<0.05$ on both sides was regarded as significant.

Results

Table 1 displays the baseline clinical and demographic characteristics of the study groups. Mean age and male incidence were similar between groups. Regarding hypertension, there was no significant difference between the groups. Diabetes mellitus and hyperlipidemia were identified more frequently in patients who developed ISR. LVEF was lower in the ISR group than in the non-ISR group. Optimal medical treatment was arranged after DES implantation and statin was initiated if not contraindicated for every patient. When medication compliance and prehospital medication before control CA were evaluated, there was no significant difference between the groups. Table 2 displays the biochemical and hematological parameters of the study groups. LDL-C and TG levels were higher and HDL-C levels were lower in patients who developed ISR. The AIP levels of patients who developed ISR were significantly higher than those who did not (0.33 [0.15-0.52] vs 0.06 [-0.08-0.21] respectively, p=0.001), as shown in Table 2 and Figure 1.

Table 1. Baseline clinical and demograhic characteristics of study group according to in-stent restonosis[a]

Variables	Total n=608	ISR (+) n=241	ISR (-) n=367	p
Age, years	60 (52-68)	59 (52-67)	60 (53-68)	0.443
Sex, male %	66.6	66.4	66.8	0.925
DM, %	46.7	54.4	41.7	0.002
Hypertension, %	70.7	70.5	70.8	0.936
Prior MI, %	51.2	60.2	45.2	<0.001
Prior CVD, %	5.4	5.8	5.2	0.719
LVEF, %	58 (45-60)	55 (45-60)	60 (50-60)	<0.001
Previous medications,%				
Aspirin	87.3	87.9	86.9	0.733
Statin	67.1	66.8	67.3	0.898
RAASi	66.0	72.6	61.6	0.005
Beta-Blocker	73.7	72.6	74.4	0.627
Insulin	18.6	23.2	15.5	0.017
OAD	41.9	48.1	37.9	0.012

[a]Data are presented as median (interquarter range) or n (%). Statistically significant p values shown in boldface; ISR: in-stent restenosis; DM: diabetes mellitus; MI: myocardial infarction; CVD: cerebrovascular disease; LVEF: left ventricular ejection fraction; RAASi: renin-angiotensin-aldesteron system inhibitors; OAD: oral antidiabetic drugs.

In Table 3, angiographic characteristics of the study groups were presented. ISR was more frequently detected in the right coronary artery. There was no significant difference between groups regarding the ISR location of other coronary arteries. Patients who developed ISR had a shorter interval between their two CA procedures than those who did not.

ROC analysis for the diagnostic accuracy of AIP in ISR patients is shown in Figure 2. The AUC value of AIP levels for predicting ISR was 0.746 (95% CI 0.705–0.787 p<0.001). Serum AIP level of 0.1678 had 70.3% sensitivity and 65.5% specificity for predicting ISR.

According to multivariate logistic regression analysis; DM (odds ratio [OR] 1.77 95% confidence interval [CI] 1.117-2.814, p=0.013), LDL-C (OR 1.024 95% CI 1.018-1.030, <0.001), LVEF (OR 0.952 95% CI 0.924-0.982, p=0.002), and AIP (OR 29.445, 95% CI 11.893-72.897, p<0.001) were determined as independent predictors of ISR (Table 4).

Discussion

In the present study, we assessed the value of AIP for predicting ISR in SAP patients who underwent successful DES implantation. The major finding of our study was that AIP levels were significantly higher in the ISR (+) group, which was an independent predictor of the development of DES-ISR in patients with SAP. Besides AIP levels; presence of HT, low LVEF and high admission LDL-C levels were also found as independent predictors of DES- ISR. To the best of our knowledge, our study is the first to show the relationship between AIP levels and DES-ISR in patients with SAP.

ISR is one of the most important complications limiting the long-term effectiveness of coronary artery stenting. The incidence of ISR has been reported over 30% following BMS implantation. DESs were evolved to overcome

Table 2. Biochemical and hematological parameters of study group according to in-stent restenosis.[a]

Variables	Total n=608	ISR (+) n=241	ISR (-) n=367	p
Glucose, mg/dL	119 (99-161)	122 (103-169)	116 (98-153)	0.044
Hgb, g/dL	13.6 (12.1-15.0)	13.8 (12.2-15.1)	13.5 (12.0-14.8)	0.019
WBC, $\times 10^9$ /L	8.0 (6.7-10.0)	8.7 (7.0-10.9)	7.8 (6.6-9.6)	<0.001
Lymphocyte	2.2 (1.6-2.9)	2.3 (1.6-3.0)	2.1 (1.6-2.7)	0.019
Neutrophil, $\times 10^9$ /L	5.0 (3.8-6.4)	5.4 (4.1-6.7)	4.7 (3.7-6.0)	<0.001
PLT count, $\times 10^9$ /L	233 (193-277)	236 (197-283)	234 (193-273)	0.194
MPV, fL	9.8 (9.0-10.6)	10.0 (9.2-10.8)	9.6 (8.9-10.4)	<0.001
Admission eGFR mL/min/1.73m^2	85.6 (69.9-102.5)	81.5 (67.0-100.6)	87.0 (71.9-104.3)	0.052
Admission Cr, mg/dl	0.87(0.76-1.07)	0.88 (0.76-1.09)	0.87 (0.74-1.05)	0.036
TSH	1.3 (0.7-2.1)	1.29 (0.73-2.02)	1.33 (0.83-2.25)	0.245
HbA1c	7.2 (6.1-8.9)	6.2 (5.7-7.4)	6.0 (5.7-7.1)	0.066
Total cholesterol,mg/dL	210 (173-243)	176 (144-208)	172 (141-210)	0.711
LDL cholesterol, mg/dL	134(98-162)	131 (108-155)	74 (59-101)	<0.001
HDL cholesterol, mg/dL	45 (39-53)	37 (32-44)	40 (34-46)	<0.001
Triglyceride, mg/dL	192 (123-287)	173 (123-272)	104 (82-138)	<0.001
AIP	0.36 (0.15-0.55)	0.33 (0.13-0.52)	0.06 (0.08- 0.21)	<0.001

[a]Data are presented as median (interquarter range) or n (%). Statistically significant p values shown in boldface. ISR: in-stent restenosis; Hgb: hemoglobin; WBC: white blood cell; PLT: platelet; MPV: mean platelet volume; eGFR: glomerular filtration rate; Cr: creatinine; TSH: thyroid stimulating hormone; HbA1c: hemoglobin A1c; LDL: low density lipoprotein; HDL: high density lipoprotein; AIP: atherogenic index of plasma.

Table 3. Baseline angiographic characteristics of study group according to in-stent restenosis.[a]

Variables	Total n=608	ISR (+) n=241	ISR (-) n=367	p
Time between the two CAG, months	32 (18-48)	28 (13-48)	33 (20-48)	0.014*
Culprit coronary artery				
Left anterior descending, %	46.5	42.7	48.9	0.136
Left circumflex, %	24.3	21.2	26.4	0.139
Right coronary artery, %	29.2	36.1	24.8	0.030

ISR: in-stent restenosis, CAG: coronary angiography; [a] Data are presented as n (%). Statistically significant p values shown in boldface.

Table 4. Logistic regression analysis to detect the independent predictors of in-stent restenosis

Variables	Univariate			Multivariate		
	OR	(95% CI)	p	OR	(95% CI)	p
AIP	30.105	14.503-62.491	<0.001	29.445	11.893-72.897	<0.001
Age	0.944	0.979-1.009	0.442	1.007	0.978-1.023	0.551
DM	1.666	1.200-2.311	0.002	1.773	1.117-2.814	0.013
LDL-C	1.026	1.021-1.031	<0.001	1.024	1.018-1.030	<0.001
LVEF	0.961	0.944-0.978	<0.001	0.952	0.924-0.982	0.002
Prior MI	1.829	1.315-2.543	0.001	1.135	0.648-1.989	0.685
Time between the two CAG	0.996	0.990-1.003	0.254	0.994	0.985-1.002	0.950

Statistically significant p values shown in boldface. OR: odds ratio; CI: confidence interval; AIP: atherogenic index of plasma; DM: diabetes mellitus; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; CAG: coronary angiography; MI: prior myocardial infarction.

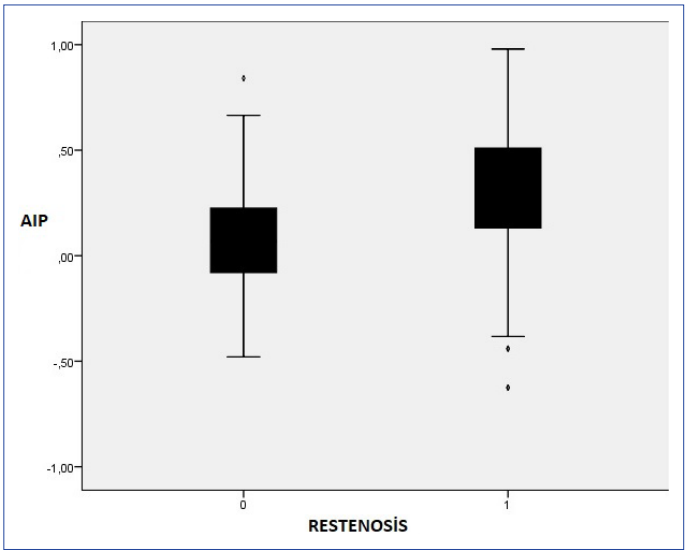

Figure 1. Comparison of levels of atherogenic index of plasma between patients with and without in-stent restenosis.

the high incidence of ISR seen after BMS implantation.[12,13] Although the incidence of ISR has decreased with the widespread use of DESs, it still remains as a serious clinical problem.[14] Although the pathogenesis of ISR after DES implantation is still controversial; biological, technical, mechanical and genetic factors have been shown to contribute to DES-ISR.[15,16]

Neoatherosclerosis has been an important factor for ISR. Neoatherosclerosis is defined by the accumulation of lipid foamy macrophages within the neointima.[13] The mechanisms that contributes to the development of atherosclerosis in native coronary arteries and in-stent atherosclerosis are different from each other. Well-known risk factors for cardiovascular diseases such as smoking, hypertension, hyperlipidemia and diabetes may not be associated with neoatherosclerosis and ISR.[17] On the other hand, Wang et al.,[18] investigated the risk factors of ISR and revealed that traditional cardiovascular risk factors such as diabetes, hypertension and high LDL-C levels were also risk factors for ISR. Similarly, we found a higher prevalence of diabetes mellitus and higher levels of LDL-C in the ISR group compared to non-ISR group. However, the prevalence of hypertension did not significantly differ between the two groups according to our results. Kuroda et al.[19] showed that high LDL-C level was a risk factor for the development of in-stent neoatherosclerosis, but they did not show the effect of hypertension on in-stent neoatherosclerosis. Likewise, there was no significant difference in the prevalence of hypertension between the groups in our study. Consistent with the literature, we found that risk factors for ISR are similar to classical risk factors of cardiovascular disease, but may differ depending on the pathogenesis.

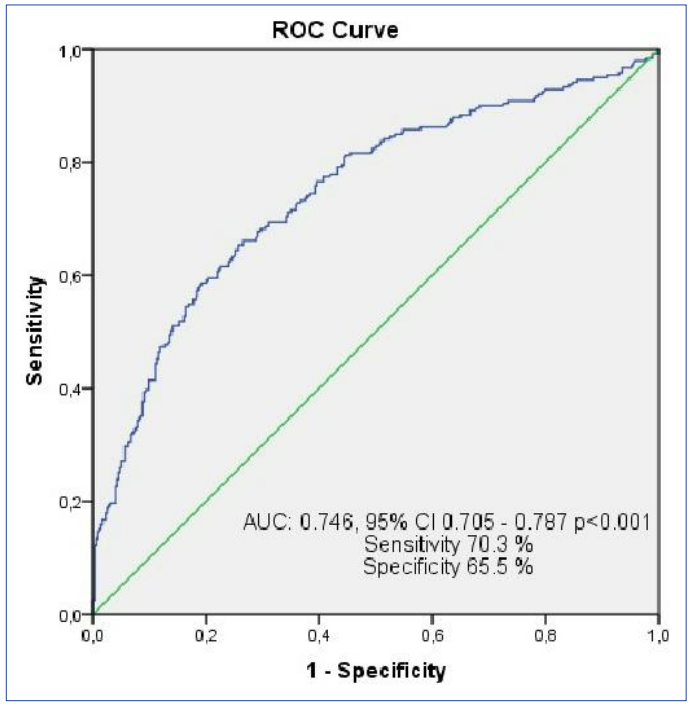

Figure 2. Receiver-operating characteristic (ROC) curve analysis of atherogenic index of plasma for predicting in-stent restenosis.

AIP is calculated by the logarithm of the molar ratio of TG to HDL-C levels. The effect of TG on atherosclerotic cardiovascular diseases has been demonstrated by recent clinical data.[20] Also, the protective feature of high levels of HDL-C in terms of atherosclerotic cardiovascular diseases is well-known.[21] AIP has been shown to be valuable in indirectly determining the level of oxidized small-dense LDL-C, which has a strong association with atherosclerotic plaque formation.[22] Being cheap, effective and easily accessible makes AIP more advantageous than other atherogenic indices. Moreover, studies have revealed that higher AIP values were associated with other risk factors of atherogenic cardiovascular disease; such as diabetes, hypertension, abdominal obesity and physical inactivity.[23-25] On this basis, it may be explained that AIP reflects the degree of metabolic impairment more comprehensively than a single parameter such as LDL-C.

The development of CAD is closely associated with lipid metabolism disorders and inflammation. Reduced HDL-C and increased LDL-C are important risk factors for ISR. Meng et al.'s[17] study revealed that high LDL-C value before CA was associated with ISR and neoatherosclerosis. Similarly, disorders in lipid metabolism provide predictive information in terms of ISR before CA in our study. Additionally, in this study, we postulate that AIP might also predict ISR, as it demonstrates the sdLDL-C level, which was not emphasized in the literature before, according to our knowledge.

Many studies have shown that AIP is a risk factor for coronary artery disease. In a study conducted by Wang et al.,[11] high AIP value was found as an independent risk factor for coronary artery disease besides classical risk factors. In the same study, it was shown that high AIP values were associated with a high SYNTAX score. Thus, the value of AIP in demonstrating the severity of coronary artery disease was demonstrated. Also, there are many studies showing the prognostic and predictive accuracy of AIP in coronary artery disease. Wu et al.[26] demonstrated the relationship between AIP and rapid progression of coronary artery disease beyond classical risk factors. This study showed that rapid plaque progression was more common at higher levels of AIP. In another study conducted by Fernández-Macías et al.,[27] it was shown that high AIP values had a strong predictive ability for CAD.

One major limitation would be the bias in patient selection as these patients were referred for repeat CAG since they had symptoms or documented ischemia. Among these patients, patients with stable angina pectoris were included in the study. Therefore, the prevalence of ISR was found to be higher than in other studies. The lack of fractional flow reserve and intravascular ultrasound evaluation in addition to coronary angiography is another limitation. Being a single-center and retrospective study with a relatively small number of patients is another limitation that hinders drawing clear conclusions about the pathophysiological relationship between AIP and DES-ISR. Lastly, the results of our study need to be replicated in larger cohorts, and the prospective follow-up investigations to better explain this relationship.

Conclusion

AIP index was higher in patients treated with DES and referred for repeat CA for recurrent symptoms. Multivariate analysis revealed that AIP was strongly independently associated with ISR. Other factors that were also related to ISR were presence of HT, DM, low LVEF and high LDL-C levels on admission. Using this novel inexpensive and easily calculable index may provide early recognition of ISR in patients with SAP who were treated with DES.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee (Ethics Committee Number: 3478 Date: 22.03.2022). This study was conducted according to the declaration of Helsinki Informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – O.S.S., K.K., G.C.; Design – O.S.S, S.S.; Supervision – K.K., K.S.; Materials – H.K., Y.D., S.S.; Data collection &/or processing – O.S.S., B.B.K.; Analysis and/or interpretation – O.S.S., K.K., K.S.; Literature search – O.S.S., H.K., E.K.; Writing – O.S.S.; Critical review – O.S.S., G.C., K.K.

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