Do pre-procedural laboratory parameters predict drug-eluting stent restenosis?

İşlem öncesi ölçülen biyokimyasal belirteçler ile ilaç kaplı stentlerde yeniden daralmayı öngörmek mümkün müdür?

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ABSTRACT

Objective: Drug-eluting stents (DES) have considerably reduced the rates of in-stent restenosis (ISR). Several studies reported pre-procedural C-reactive protein (CRP), neutrophil to lymphocyte (N/L) ratio, red cell distribution width (RDW), serum uric acid (UA), and mean platelet volume (MPV) as independent predictors of ISR using bare metal stents. This study investigates whether any laboratory parameter obtained before the coronary stenting procedure is associated with ISR using DES in stable coronary artery disease.

Methods: Three hundred fifteen stents were retrospectively analysed in 285 patients who had undergone coronary stenting and a control coronary angiography within one year of stenting, between January 2012 and April 2014. Pre-procedural complete blood count, biochemistry, and CRP were recorded. Off-line quantitative coronary angiography analysis was performed.

Results: Overall restenosis rate was 10.2%. When the stents were analysed with respect to the presence of ISR, the number of diabetics and smokers was higher in the ISR group. CRP levels were significantly higher in the ISR group, but there were no differences in N/L, monocytes, eosinophils, RDW, MPV, UA, and total bilirubin levels. In the univariate regression analysis, DM, CRP, stent length, stent diameter, pre-procedural diameter stenosis, pre-procedural minimal lumen diameter (MLD), post-procedural residual diameter stenosis, post-procedural reference vessel diameter, and post-procedural MLD were predictors of ISR. However, multivariate regression analysis identified only DM and post-procedural residual stenosis as independent predictors of ISR.

Conclusion: Pre-procedural blood parameters do not independently predict ISR in DES, which is mainly determined by the presence of diabetes and post-procedural residual stenosis.

ÖZET

Amaç: İlaç kaplı stentler, stent içi yeniden daralma oranlarını önemli ölçüde azaltmıştır. Çeşitli çalışmalarda C-reaktif protein (CRP), nötrofil/lenfosit oranı (N/L), eritrosit dağılım genişliği (RDW), serum ürik asit (ÜA) düzeyleri, ortalama trombosit hacmi (MPV) gibi kanda ölçülen bazı parametreler çıplak metal stentlerde yeniden daralmanın öngördürücüleri olarak saptanmıştır. Bu çalışmada kararlı koroner arter hastalığında ilaç kaplı stent uygulamasında işlem öncesi kanda ölçülen herhangi bir parametre ile yeniden daralma arasında ilişki araştırıldı.

Yöntemler: Ocak 2012 ve Nisan 2014 tarihleri arasında koroner stent yerleştirilen ve sonraki bir yıl içinde kontrol koroner anjiyografisi yapılan 285 hastadaki 315 stent geriye dönük olarak incelendi. İşlem öncesi tam kan sayımı, rutin biyokimyasal incelemeler ve CRP düzeyleri kaydedildi. Koroner anjiyografik değerlendirme kantitatif koroner anjiyografi ile yapıldı.

Bulgular: Genel yeniden daralma oranı %10.2 idi. Stentler stent içi yeniden daralma varlığı bakımından analiz edildiğinde, yeniden daralma grubunda diyabetik ve sigara içenler daha fazlaydı; CRP düzeyleri daha yüksekken N/L, RDW, eozinofil, monosit, MPV, ÜA, total bilirubin düzeyleri bakımından fark yoktu. Tek yönlü regresyon analizinde, diyabet, CRP, stent uzunluğu ve çapı, işlem öncesi daralma yüzdesi, işlem öncesi en düşük lümen çapı, işlem sonrası rezidüel daralma yüzdesi, işlem sonrası referans damar çapı ve en düşük lümen çapı stent içi yeniden daralmanın öngördürücüleriydi. Çok değişkenli regresyon analizinde ise sadece diyabet ve işlem sonrası rezidüel daralma yüzdesi bağımsız öngördürücüler olarak saptandı.

Sonuç: İlaç kaplı stentlerde yeniden daralmayı öngörmede işlem öncesi kanda bakılan hiçbir parametrenin yararı olmamıştır; ancak, diyabet ve işlem sonrası rezidüel darlık miktarı esas belirleyiciler olarak ön plana çıkmıştır.

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In-stent restenosis (ISR) is a significant problem, affecting up to 30% of patients in the era of bare-metal stents (BMS).[1] Stent implantation causes injury in the coronary vessel endothelium, initiating both local and systemic inflammatory responses, which play an important role in the pathophysiology of ISR.[2,3] Patient-dependent factors, clinical conditions in which the patient undergoes the procedure, technical details, and characteristics of the lesion constitute the spectrum of variables which lead to ISR. Drug-eluting stents (DES) have improved outcomes by reducing neointimal hyperplasia, thus reducing the rate of ISR to less then 10%[4,5] and reducing repeat revascularization procedures.[6]

Several studies investigated whether laboratory parameters measured by complete blood count or biochemical analysis before the coronary stenting procedure could predict ISR. Red cell distribution width (RDW),[7] neutrophil to lymphocyte (N/L) ratio,[8] mean platelet volume (MPV),[9] serum uric acid levels (UA),[10] and serum C-reactive protein levels (CRP)[11] were found to be associated with ISR. Most of these studies were performed using BMS.

The purpose of this study was to investigate whether any readily-available parameter measured by a simple blood draw before the coronary stenting procedure could be associated with in-stent restenosis using drug-eluting stents in patients admitted with stable coronary artery disease (CAD).

METHODS

This is a retrospective study analysing the hospital records of patients with stable angina pectoris or angina equivalent symptoms who were admitted to the cardiology outpatient clinic of a university hospital and decided to undergo coronary angiography and elective stenting after appropriate non-invasive tests were performed. Inclusion criteria included age (range: 18–80), elective coronary stenting with 2nd generation DES (Zotarolimus eluting Resolute Integrity [Medtronic Inc. Santa Rosa, CA, USA] or Biolimus eluting BioMatrix [Biosensors Europe SA, Switzerland]) due to stable CAD, stored quantitative coronary angiography (QCA) data prior to stenting showing the percentage of luminal narrowing >70% (nearly all final decisions in the cardiology clinic regarding performing a stenting procedure and the choice of stent length and diameter in elective cases are based on QCA analysis after an initial visual assessment), and a control angiography after the initial stenting procedure within 1 year (routine control angiography performed 6 months - 1 year after stenting, is the standard practice in our institution).

Abbreviations:

BMS	*Bare-metal stents*
CAD	*Coronary artery disease*
CRP	*C-reactive protein*
DES	*Drug-eluting stents*
ISR	*In-stent restenosis*
MLD	*Minimal lumen diameter*
MPV	*Mean platelet volume*
N/L	*Neutrophil to lymphocyte ratio*
QCA	*Quantitative coronary angiography*
RDW	*Red cell distribution width*
RVD	*Reference vessel diameter*

Exclusion criteria consisted of history of coronary artery by-pass graft operation, left-main lesion, chronic total occlusion, BMS or first generation DES, in-stent restenosis, acute or chronic infection during the initial procedure, malignancy, anemia, recent blood transfusion, renal insufficiency, hepatic insufficiency, hypo- or hyperthyroidism, and any rheumatologic, immunologic or inflammatory disorders. In addition, patients who received polymer-free DES were excluded because the polymer-free structure could possess different properties with respect to in-stent restenosis than the polymer-based stents used in this study, which sought to avoid a heterogeneous study population with respect to the nature of the stents implanted.

All percutaneous coronary intervention procedures with stenting performed between January 2012 and April 2014 were consecutively analysed in terms of inclusion and exclusion criteria, after which 315 eligible patients were enrolled to the study. This study was conducted according to the recommendations of the Declaration of Helsinki on Biomedical Research involving human subjects and was approved by the institutional ethics committee.

All coronary stenting procedures were performed through femoral artery by standard techniques with 7 Fr guiding catheters using GE Innova 4100 cath laboratory (GE Healthcare, Milwaukee, WI, USA). Two-dimensional quantitative coronary angiography (QCA) analysis was performed off-line using QCA software package (QAngio XA 7.3; Medis Medical Imaging Systems BV, Leiden, Netherlands). Lesion length, percentage diameter stenosis, minimal lumen diameter (MLD), and reference vessel diameter (RVD) of the treated coronary segment before and

after the stent implantation were determined via imaging in which the lesion was most severe and not foreshortened. Zotarolimus-eluting Resolute Integrity (Medtronic Inc. Santa Rosa, CA, USA) or Biolimus eluting BioMatrix (Biosensors Europe SA, Switzerland) were implanted in coronary vessels with a luminal narrowing >70%, as determined by QCA. Each patient received acetyl salicylic acid (ASA) and clopidogrel (300 mg loading dose) before the procedure. Unfractionated heparin 100 U/kg was administered at the beginning of the procedure to maintain activated clotting time >250 seconds. Choice of stent, predilatation or postdilatation of the stent, and use of glycoprotein IIb/IIIa inhibitors were determined by the operator. Successful PCI was defined as TIMI grade III flow without any major complications with a residual stenosis <20% by visual estimation. All patients were prescribed ASA 100 mg indefinitely and clopidogrel 75 mg for ≥1 year. Stent restenosis was concluded according to the QCA analysis of the control coronary angiography and defined as >50% narrowing in a vessel including 5 mm proximal and distal to the stent edge. Restenosis pattern was defined as focal when the luminal narrowing was <10 mm in length, and diffuse when it was ≥10 mm in length. The data was analysed by two cardiologists, with a third cardiologist consulted in the case of discrepancy.

Clinical and demographic data of patients—including age, presence of hypertension, diabetes, hyperlipidemia, and smoking status—were noted from the hospital records. All laboratory data at the time of initial stenting procedure were also recorded. Laboratory data, which was measured by immunoturbidimetric assay (Abbott Architect c8000, USA), consisted of complete blood count (Cell-Dyn 3700, Abbott, USA) and biochemistry (Unicel Dx C800 Synchron, Beckman Coulter, USA), including kidney function tests, hepatic function tests, serum UA levels, lipid profile and CRP. These data were obtained from venous blood samples which were drawn upon 12 hours of fasting before the coronary stent implantation.

Statistical analyses

Statistical analyses were performed using SPSS statistical software (IBM SPSS Statistics 21). Shapiro-Wilk test was performed for distribution pattern. Categorical variables were expressed as percentages, whereas continuous variables were presented as mean±standard deviation. Continuous variables were compared by Student's t-test and Mann-Whitney U tests. χ^2 test was used for the categorical variables between the two groups. Univariate and multivariate regression analysis was performed in order to identify the determinants of ISR. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$.

RESULTS

Table 1 shows basal characteristics of the study population. Mean age was 65.3±10.5, and 65% of the patients were male. Rate of diabetics was 41.9%. According to ACC/AHA lesion classification, 49.5% of the lesions were of type B, whereas 40.3% were of type C. Restenosis rate was 10.2%.

Table 1. Baseline characteristics of the study population

	%	Mean±SD
Age		65.3±10.5
Sex (male)	65.0	
Hypertension	66.6	
Diabetes mellitus	41.9	
Hyperlipidemia	64.4	
Family history of CAD	40.7	
Smoker	46.7	
Target vessel		
LAD	37.8	
LAD-diagonal	3.8	
Cx (%)	20.6	
Cx-OM	5.7	
RCA	32.1	
Lesion length (mm)		17.1±7.6
Lesion type (ACC/AHA)		
A	10.2	
B	49.5	
C	40.3	
#Stent per lesion		1.1±0.4
Stent length (mm)		19.6±8.2
Stent diameter (mm)		3.1±0.3
Restenosis	10.2	
Focal	3.8	
Diffuse	6.4	

#: Number of. CAD: Coronary artery disease; LAD: Left anterior descending; Cx: Circumflex; RCA: Right coronary artery.

When analysed with respect to the presence of ISR, the ISR group contained more patients who were diabetic and smokers than in the non-ISR group. Serum creatinin and CRP levels were significantly higher in the ISR group. Serum uric acid levels were 5.7±1.4 and 5.3±1.3 in the ISR and non-ISR groups, respectively; however, this result did not reach statistical significance. There were no significant differences between the two groups with respect to N/L ratio, monocyte count, eosinophil count, RDW, MPV, and total bilirubin levels (Table 2).

Table 3 demonstrates the angiographic parameters obtained by QCA related to the coronary lesion and

Table 2. Demographic, clinical characteristics and laboratory measurements with respect to the presence of in-stent restenosis

	No-ISR (n=283)		ISR (n=32)		*p*
	%	Mean±SD	%	Mean±SD	
Demographic and clinical characteristics					
Age (years)		65.6±10.4		62.7±11.2	0.13
Gender (Male/Female)	64.0/36.0		81.3/18.8		0.04
Hypertension	66.8		59.4		0.43
Diabetes mellitus	39.6		62.5		0.01
Hyperlipidaemia	64.0		68.8		0.69
Smoker	43.8		71.9		0.03
Laboratory measurements					
Fasting plasma glucose (mg/dl)		108.7±26.9		121.0±39.7	0.08
Hemoglobin (g/dl)		13.3±0.9		13.4±1.1	0.79
Red cell distribution width (%)		15.7±1.9		15.2±1.7	0.26
White blood cell count ($10^3/\mu l$)		6.2±1.1		5.9±0.9	0.12
Neutrophil count ($10^3/\mu l$)		3.2±0.7		3.5±0.8	0.11
Lymphocyte count ($10^3/\mu l$)		1.5±1.4		1.6±0.5	0.12
Neutrophyl-lymphocyte ratio		2.30±0.72		2.33±0.83	0.81
Monocyte count ($10^3/\mu l$)		0.58±0.20		0.59±0.22	0.06
Eosinophil count ($10^3/\mu l$)		0.24±0.15		0.25±0.14	0.1
Platelet count ($10^3/\mu l$)		281.5±61.1		273.3±67.4	0.56
Mean platelet volume (fl)		7.2±0.5		7.3±0.6	0.43
Blood urea nitrogen (mg/dl)		27.6±4.2		29.8±4.7	0.09
Creatinine (mg/dl)		0.9±0.3		1.1±0.3	0.04
Uric acid (mg/dl)		5.3±1.3		5.7±1.4	0.08
High-density lipoprotein cholesterol (mg/dl)		40.5±7.5		39.9±7.1	0.62
Low-density lipoprotein cholesterol (mg/dl)		138.1±13.6		139.6±11.7	0.33
Triglyceride (mg/dl)		173.8±35.7		183.6±34.2	0.05
C-reactive protein (μg/ml)		3.4±0.9		3.8±0.9	0.01
Total bilirubin (mg/dl)		0.93±0.22		0.91±0.25	0.51
Gamma-glutamyl transferase (mg/dl)		31.9±4.1		33.6±4.2	0.06
Aspartate aminotransferase (mg/dl)		25.4±4.1		26.3±4.3	0.11
Alanine aminotransferase (mg/dl)		25.4±3.9		26.5±4.3	0.07
Alcaline phosphatase (mg/dl)		81.6±18.6		74.1±20.4	0.06

p<0.05 is considered as statistically significant.

Table 3. Angiographic parameters with respect to the presence of in-stent restenosis

	Non-ISR (n=283)		ISR (n=32)		*p*
	%	Mean±SD	%	Mean±SD	
Lesion location					0.488
Left anterior descending	38.5		31.3		
Left anterior descending-diagonal	3.9		3.1		
Circumflex	20.8		18.8		
Circumflex-OM	4.9		12.5		
Right coronary artery	31.8		34.4		
Lesion length (mm)		16.77±7.44		19.78±8.94	0.064
Lesion type					0.033
A	10.6		6.3		
B	51.2		34.4		
C	38.2		59.4		
#Stent implanted per lesion		1.09±0.33		1,25±0.50	0.009
Stent length (mm)		19.19±7.94		22.78±9.66	0.040
Stent diameter (mm)		3.08±0.31		2.94±0.24	0.006
Pre-PCI reference vessel diameter (mm)		2.92±0.32		2.75±0.26	0.002
Post-PCI reference vessel diameter (mm)		3.19±0.32		2.99±0.26	0.001
Pre-PCI minimal lumen diameter (mm)		0.84±0.31		0.67±0.24	0.002
Post-PCI minimal lumen diameter (mm)		3.12±0.33		2.82±0.26	<0.001
Pre-PCI stenosis (%)		83.14±10.26		87.53±9.23	0.022
Post-PCI stenosis (%)		1.77±2.86		5.93±3.93	<0.001

PCI: Percutaneous coronary intervention, #: Number of, p<0.05 is considered as statistically significant.

stent implanted. The percentage of type C lesions was higher in the ISR group (59.4% *vs.* 38.2%, p=0.033). Mean stent length and number of stents implanted per lesion were higher in the ISR group, whereas mean stent diameter was lower. When QCA data were compared, pre-procedural and post-procedural mean RVD and MLD were lower in the ISR group, while pre-procedural and post-procedural percentages of diameter stenosis were higher in the ISR group.

Table 4 shows the results of logistic regression analysis. In the univariate regression analysis (Table 4), DM, serum CRP levels, stent length, stent diameter, pre-PCI diameter stenosis, pre-PCI MLD, post-PCI diameter stenosis (residual stenosis), post-PCI RVD, and post-PCI MLD were predictors of ISR. Nonetheless, multivariate regression analysis identified only DM and post-PCI diameter stenosis (residual stenosis) as independent predictors of ISR (Table 5).

DISCUSSION

We analysed whether any routinely measured hematologic or biochemical parameter might be used as a predictor of ISR in stable CAD in the era of 2nd generation DES. Serum CRP level was identified as an ISR predictor in the univariate regression analysis. However, multivariate regression analysis revealed that only the presence of DM and post-PCI residual stenosis were significant predictors of ISR using 2nd generation DES in stable patients.

In this study, we detected an overall restenosis rate of 10.2%. This is a slightly high rate considering the use of DES; nevertheless, had we restricted coronary angiography procedures only to symptomatic patients, a lower restenosis rate may have been reported. Routine coronary angiography after 6–8 months of stent restenosis remains controversial. In the 2012 appropriate use criteria for diagnostic coronary angiog-

Table 4. Univariate logistic regression analysis to determine the predictors of in-stent restenosis

	OR	95% CI	*p*
Age	0.97	0.941–1.008	0.135
Male sex	2.44	0.973–6.129	0.057
Diabetes mellitus	2.54	1.197–5.410	0.015
Stent length	1.04	1.006–1.083	0.023
Stent diameter	0.19	0.046–0.781	0.021
Pre-percutaneous coronary intervention reference vessel diameter	1.16	0.048–0.621	0.124
Pre-percutaneous coronary intervention minimal lumen diameter	0.16	0.045–0.568	0.005
Pre-percutaneous coronary intervention percentage of stenosis	1.05	1.006–1.085	0.024
Post-percutaneous coronary intervention reference vessel diameter	0.11	0.028–0.405	0.001
Post-percutaneous coronary intervention minimal lumen diameter	0.03	0.007–0.140	<0.001
Post-percutaneous coronary intervention percentage of stenosis	1.37	1.235–1.524	<0.001
C-reactive protein	1.80	1.163–2.774	0.008

CI: Confidence interval; OR: Odds ratio. p<0.05 is considered as statistically significant.

Table 5. Multivariate logistic regression analysis to determine the predictors of in-stent restenosis

	OR	95% CI	*p*
Diabetes mellitus	2.76	1.084–7.070	0.033
Post-percutaneous coronary intervention percentage of stenosis	1.43	1.121–1.838	0.004

CI: Confidence interval; OR: Odds Ratio. p<0.05 is considered as statistically significant.

raphy, routine control angiography after stenting was considered unnecessary, unless there were symptoms or signs of ischemia.[12] However, in a recently published study conducted on a large cohort of 10,004 patients, presence of restenosis at follow-up angiography predicted 4-year mortality, and prognostic value was maintained in asymptomatic patients as well as symptomatic patients.[13]

In a retrospective study of 624 patients who had undergone PCI with BMS due to stable or unstable angina pectoris, pre-procedural N/L ratio was a strong and independent predictor of restenosis.[8] Serum UA, which is associated with atherosclerosis as a result of proinflammatory properties, was also found to be a strong predictor of ISR in BMS in patients with stable and unstable pectoris.[10] CRP is a well-studied marker of systemic inflammation and was found to be related to atherosclerotic events.[14] It was shown to be a significant predictor of angiographic BMS restenosis in a meta-analysis including 2,747 patients.[15] Inflammation is undoubtedly an important pathogenetic mechanism of stent restenosis. Monocytes, neutrophils, and Th1 lymphocytes primarily result from classical inflammatory response; however, eosinophils and Th2 lymphocytes result from allergic inflammation, which is a pathogenetic mechanism in DES but not BMS.[1] Hypersensitivity reactions to the polymer employed in DES underlie allergic inflammation. Although blood eosinophil or monocyte count does not reflect the amount of inflammatory infiltrate in the stented segment, we nonetheless compared their levels between ISR and non-ISR patients. No significant differences were found.

In BMS restenosis, the main process is neointimal proliferation. This is characterized by smooth muscle cell proliferation and extracellular matrix synthesis, which are driven by arterial inflammation caused by the medial damage and/or penetration of the stent struts into the lipid core of atherosclerotic plaques.[16] Intimal hyperplasia after BMS usually peaks between 6 months–1 year, after which a quiescent period resumes.[17,18] The mechanism for DES restenosis includes different aspects. Chronic inflammation and impaired endothelial function cause late de novo neo-

atherosclerosis in both BMS and DES; however, this occurs earlier and with greater frequency in DES.[19] Hypersensitivity reaction to the employed polymer is another pathogenetic mechanism of ISR in DES.

Elevated CRP levels were associated with stent thrombosis, death, myocardial infarction, and stroke in patients receiving DES.[20,21] Although pre-procedural CRP was an independent predictor of adverse cardiac events, it was not detected as a predictor of stent restenosis with DES. Park et al. showed that while event-free survival was decreased in patients with higher pre-procedural CRP levels who received DES, restenosis rates were not significantly different in the lowest and highest tertiles of CRP.[22] In addition, pre-procedural CRP was not correlated with the degree of diameter stenosis, MLD, or late lumen loss at follow up. In light of these findings, it can be supposed that the association between CRP and adverse events reported in those studies may be attributed to stent thrombosis rather than stent restenosis, considering that higher inflammatory activity is associated with increased platelet and clotting cascade activity.[23] In our study, CRP levels were higher in patients with ISR, and it was a predictor of ISR in univariate but not multivariate regression analysis.

Studies describing associations between serum CRP, N/L ratio, serum UA levels, MPV, and RDW are typically performed with BMS. We have not detected any differences with respect to N/L ratio or serum UA levels in patients with or without ISR. This discrepancy is probably due to the difference between the study designs. Our study population consisted of patients only with stable CAD, and we used 2nd generation DES. Anti-proliferative and anti-inflammatory effects of the drugs might have prevented us from detecting any inflammatory marker as a predictor of DES ISR.

Kurtul et al. reported that RDW predicted ISR in BMS stable CAD patients.[7] They concluded that immaturation of red blood cells from inflammatory cytokines which cause heterogeneity in RBC size, and oxidative stress which also causes heterogeneity in RBC size were the factors which raised RDW as a predictor of ISR. However, our results differed from that study, as we found similar RDW levels in both ISR and non-ISR patients.

The main limitation of the study was the retrospective design, which prevented us from inferring causality. We were not able to serially measure blood levels of the parameters mentioned. There may have been uncontrolled factors which affected the results. In addition, we did not have IVUS or optical coherence tomography data to illustrate the morphology in the stented segment. Control angiography was performed within 1 year of the stenting procedure. Longer-term angiographic results might be different, considering the possibility of later neointimal proliferation with DES[24] and late de novo neoatherosclerosis.[19]

Long-term prospective studies performing control coronary angiography—preferably with IVUS—and obtaining serial measurements of all hematologic, biochemical and inflammatory markers of interest would be beneficial in determining whether these parameters are significant predictors of ISR in DES.

In conclusion, in stable CAD when 2nd generation DES was used, patient-related factors and procedural factors were of paramount importance. None of the pre-procedural blood parameters could be safely used to predict future ISR.

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Key words: Drug-eluting stent; in-stent restenosis; predictors of restenosis.

Anahtar sözcükler: İlaç kaplı stent; stent içi yeniden daralma; yeniden daralma öngördürücüleri.