Risk factors associated with intra-stent restenosis after percutaneous coronary intervention

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Abstract. The present study aimed to explore the correlations between clinical, biological, imagistic and procedural factors with the risk of intra-stent restenosis (ISR) in coronary artery disease (CAD) patients after percutaneous coronary intervention (PCI). An observational cross-sectional study was conducted in a high-volume PCI center over a period of 2 years. A total of 235 consecutive patients diagnosed with angina or acute coronary syndrome treated by PCI were included in the study. Diagnosis of ISR was documented by coronary angiography in patients with suggestive coronary symptoms and ischemic changes in non-invasive or invasive paraclinical investigations. Thus, they were assigned to two groups: With or without ISR. All patients underwent clinical and laboratory examination, providing clinical and paraclinical variables that could be considered risk factors for ISR. Current smokers [risk ratio (RR)=1.63; 95% confidence interval (95% CI): 1.25-2.13], arterial hypertension (RR=1.86; 95% CI: 1.41-2.45), diabetes (RR=1.83; 95% CI: 1.42-2.36), high C-reactive protein (CRP) levels (RR=1.44; 95% CI: 0.93-2.24), chronic kidney disease (CKD) (RR=1.90; 95% CI: 1.53-2.36) and thrombolysis in myocardial infarction (TIMI) score were found to have a significant role in estimating the risk for ISR. Moreover, the ISR group (119 patients) presented with a lower stent inflation pressure when compared to the control group (116 patients) (14.47 vs. 16.14 mmHg, P=0.004). An increased mean stent diameter used for PCI was not associated with a high ISR incidence (P=0.810) as well as complex coronary treated lesions with longer stents (mean length of 24.98 mm in patients without ISR vs. 25.22 mm in patients with ISR; P=0.311). There was an estimated two times higher risk (RR=2.13; 95% CI: 1.17-3.88) concerning multi-stenting and restenosis degree >70%. To conclude, smoking, hypertension, diabetes mellitus, high CRP levels, CKD, TIMI score, stent type, low pressure for stent implantation and multi-stenting were found to be associated with ISR in patients following PCI. Therefore, a close follow-up should be targeted in such patients.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide while atherosclerotic coronary artery disease (CAD) is mainly involved (1). After performing percutaneous coronary intervention (PCI), patients are still at risk of developing new stenosis, such as intra-stent restenosis (ISR). The treatment of patients with ISR represents an important clinical problem and is still considered a challenge (2-4). Despite the proven safety and efficacy of drug-eluting stents (DES) in patients undergoing PCI, bare-metal stents (BMS) are still widely used as well, mainly because of their reduced cost and concerns about a debatable increased risk of bleeding associated with prolonged dual antiplatelet therapy after DES (5,6). In addition, neoatherosclerosis is associated more often with 1st generation DES than with BMS and occurs several months/years following PCI, while atherosclerosis in native coronary arteries develops over decades (7).

The incidence of ISR is still significant when considering either DES or BMS for patients following PCI (8,9), mainly because inflammatory responses after PCI lead to abnormal neointimal healing and thus generate a higher risk of unfavorable outcomes (7). This suggests that the type of stent is only one factor to consider when searching for additional promoters of ISR. In fact, the results of previous research conclude that the factors associated with ISR after PCI have not been clearly defined. Thus, the present study aimed to detect the clinical, biological, imagistic and procedural factors associated with ISR.

Patients and methods

Patient selection and study design. The design of our study was observational, cross-sectional, over a 2-year period, from

a single high-volume PCI center. A total of 235 consecutive patients who were diagnosed with angina pectoris or acute coronary syndrome (myocardial infarction with or without ST elevation) treated by PCI, were included. Our study population was divided into 2 groups: Experimental group (119 patients) that presented ISR documented by coronary angiography (>50% stenosis of a previously stented segment) and the control group (116 patients) without angiographic ISR, but with different other culprit lesions or no significant angiographic stenosis.

Patients were eligible for the study if they were ≥18 years and presented with a diagnosis of angina pectoris or acute myocardial infarction previously treated by stent implantation. Patients were not eligible for the study if they refused or abandoned treatment, if they did not report for the control visit or if they were part of a vulnerable category (e.g., pregnant women, patients in coma). The study was approved by the University of Medicine and Pharmacy 'Grigore T. Popa' Iasi Research Ethics Committee, and all subjects had initially agreed and signed an informed consent in order to take part in this study.

Clinical and paraclinical characteristics. Diagnosis of ISR was documented by coronary angiography in patients with suggestive coronary symptoms and ischemic changes in non-invasive or invasive paraclinical investigations. All patients underwent clinical and laboratory examination, providing a large number of variables that could be considered risk factors for ISR: i) clinical variables: age, sex, smoking, hypertension, diabetes, obesity, chronic kidney disease (CKD; creatinine clearance <60 ml/min), acute renal failure, thrombolysis in myocardial infarction (TIMI) score; ii) paraclinical variables: left ventricular ejection fraction (LVEF), albuminuria, LDL cholesterol, erythrocyte sedimentation rate (ESR), creatinine clearance, uric acid, C-reactive protein (CRP), fibrinogen; iii) coronary anatomical variables: left main (LM), left anterior descending (LAD), left circumflex artery (LCX), right coronary artery (RCA); and iv) variables depending on the procedure: type, length and diameter of stent and pressure under which the stent was implanted.

Statistical analysis. Data analysis was performed using SPSS 20.0 (Statistical Package for the Social Sciences; IBM Corp.). Comparison between the 2 groups of patients was performed using Chi-square test for the categorical data and one-way ANOVA and Student's t-test for continuous data. When a normal distribution was not present for continuous variables, Mann Whitney/Kruskal-Wallis tests were used. In order to estimate the strength of the association between risk factors and outcome (with or without ISR) relative risk (RR) with 95% confidence interval (CI) was used in the statistical analysis of the data. A P-value <0.05 was considered statistically significant.

Results

The mean age of the patients was 61.84±11.12 years (63.08 years, ISR group; 60.57 years, non-ISR group; P=0,084). Factors associated with ISR are presented in Tables I and II. Smoking, hypertension, diabetes, high CRP levels, CKD and TIMI score were found to be significantly associated with ISR in this group of patients. All these factors influenced the risk via a directly proportional relationship. Regarding the endothelial dysfunction markers, the cut-off values were calculated in order to establish the risk associated with them: ESR=30 mm/h, uric acid=5 mg/dl, creatinine clearance=5 ml/min, CRP=2 mg/dl, fibrinogen=400 mg%. Analyzing both study groups, approximately 44% of the patients had an LDL value >100 mg/dl.

Our study showed a 60.9% use of BMS with a more significant frequency in patients with ISR (73.1 vs. 48.3%, P=0.001), suggesting the high importance that should be given to the type of stent used for PCI. Comparing the 2 types of stent, the data for DES implantation were more consistent and well-described. Assessing the presence of restenosis events in patients that suffered stent implantation in the first 8 h after myocardial infarction, BMS implantation was directly linked to restenosis events over a period of 1-12 months and also >12 months, while DES implantation showed no significant restenosis events over the follow-up period (Fig. 1). Furthermore, early ISR (during the first month after PCI) was observed only in patients with BMS regardless of the time the stent was implemented, followed by a higher incidence of ISR in patients with BMS vs. DES after a 1-month period (1-12 months: 27.3 vs. 14.1%; >12 months: 31.5 vs. 20.7%) (Table III).

Furthermore, our study aimed to identify if there is a correlation between restenosis and various specific variables: The pressure under which the stent was deployed, the diameter of the stent or the length of the stent. The mean stent inflation pressure was significantly lower in patients with BMS implantation. Thus, the ISR group presented a lower pressure when compared to the control group (14.47 vs. 16.14 mmHg, P=0.004). Although the mean stent inflation pressure did not correlate with the time course of restenosis, the level was slightly lower in patients with ISR after 12 months compared to patients with no restenosis (14.65 vs. 15.56; P=0.628) (Fig. 2).

Moreover, an increased stent diameter used for PCI in our patients did not resonate with a high ISR incidence (mean stent diameter was 3.24 mm in patients without ISR vs. 3.22 mm in patients with ISR; P=0.810) (Fig. 3). Analyzing the length of the stent, our study revealed a slight ISR increase in patients with complex coronary lesions that implied longer stents (mean length 24.98 mm in patients without ISR vs. 25.22 mm in patients with ISR; P=0.311) (Fig. 4). Also, the correlation between multi-stenting and restenosis degree >70% was statistically significant (63 vs. 29.6%; P=0.004), indicating an estimated 2 times higher risk (RR=2.13; 95% CI: 1.17-3.88) (Fig. 5).

Discussion

The main finding of the present study is that ISR in patients following PCI is associated with smoking, hypertension, type 2 diabetes, CKD, TIMI score, the type of stent, low inflating stent pressure and multi-stenting. Patients were screened for clinical and paraclinical characteristics, coronary-lesion related factors and stent-related factors. Studies are controversial concerning the risk of ISR in patients after PCI, thus further research in larger cohort studies is needed.

Smoking continues to represent a major health risk factor with a significant contribution to cardiovascular morbidity and

Table I. Summary of the general factors associated with ISR.

Variable	ISR group (n=119) n (%)	Non-ISR group (n=116) n (%)	P-value	RR	95% CI
Sex					
Male	83 (70)	81 (70)	0.989		
Female	36 (30)	34 (30)	0.522		
Age ≥60 years	77 (64.7)	64 (55.2)	0.125		
Current smokers	74 (62.2)	44 (37.9)	**0.001**	1.63	1.25-2.13
Hypertension	72 (62.1)	38 (31.9)	**0.001**	1.86	1.41-2.45
Diabetes mellitus	68 (57.1)	31 (26.7)	**0.001**	1.83	1.42-2.36
Obesity	35 (29.4)	27 (23.3)	0.285	1.16	0.89-1.52
LDL cholesterol >70 mg/dl	91 (76.5)	93 (80.2)	0.596	1.05	0.95-1.20
ESR >30 mm/h	48 (40.3)	37 (31.9)	0.178	1.19	0.93-1.53
Uric acid >5 mg/dl	30 (71.4)	23 (60.5)	0.303	1.27	0.79-2.07
Creatinine clearance <75 ml/min/1.73 m^2	27 (44.3)	31 (47.7)	0.699	0.93	0.65-1.34
CRP >2 mg/dl	94 (87.0)	83 (77.6)	**0.050**	1.44	0.93-2.24
Fibrinogen >400 mg/dl	84 (70.6)	72 (62.6)	0.195	1.20	0.90-1.60
Albuminuria	16 (13.4)	19 (16.4)	0.528	0.89	0.60-1.31
CKD	43 (36.1)	11 (9.5)	**0.001**	1.90	1.53-2.36
Acute renal failure	7 (5.9)	5 (4.3)	0.583	1.16	0.71-1.91

ISR, intra-stent restenosis; RR, risk ratio; CI, confidence interval; LDL, low density lipoprotein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CKD, chronic kidney disease. Significant P-values are indicated in bold print.

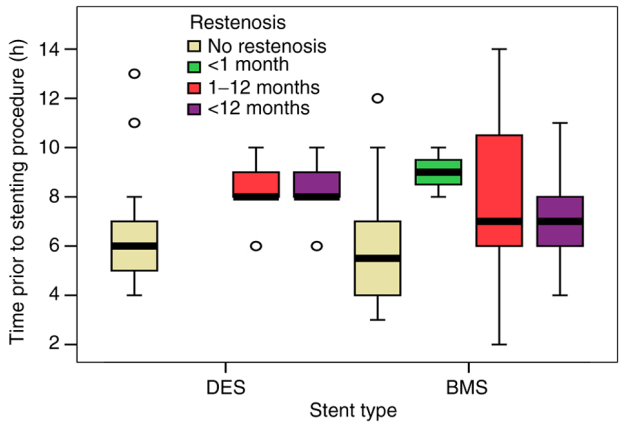

Figure 1. Correlation between type of stent, time prior to stenting procedure and time course of restenosis. DES, drug-eluting stents; BMS, bare-metal stents.

mortality. A recent meta-analysis performed on 141 cohort studies and 55 study reports concluded that smoking one cigarette per day carries around half of the risk than for those smoking 20 cigarettes per day (10). In our study, smoking represents an important risk factor that leads to CAD and also to post-PCI ISR.

Our results demonstrated that the estimated risk induced by arterial hypertension was higher in patients without ISR (RR=1.86; 95% CI: 1.41-2.45; P=0.001). Our findings are in accordance with other studies that have identified a positive correlation between hypertension and ISR. In a retrospective study that included 289 patients, Wihanda *et al* identified hypertension as a risk factor associated with ISR in patients following PCI (11). Moreover, Mohan and Dhall found a significant and positive correlation between hypertension and ISR (12).

There is still a lack of clarity in describing the exact mechanism that promotes the risk of ISR in patients with diabetes, but a recent animal laboratory study revealed that insulin and, moreover, insulin receptors are primarily responsible for the accelerated intimal hyperplasia in diabetes which is directly linked to the restenosis phenomenon. These results are surprising, considering multiple previous studies that imply a more important effect of another factor, the insulin-like growth factor-1 (13). The physiopathological mechanism presented in the literature and the higher incidence of diabetes in our patients with ISR compared to those without confirm the inclusion of diabetes mellitus in the group of risk factors for ISR.

The endothelial dysfunction responsible for ISR is determined by an inflammatory status in patients with CAD. C-reactive protein (CRP) is recognized as an important marker for systemic inflammation and for predicting cardiovascular events, therefore it can be used in primary and secondary prevention. The cut-off value for CRP in our study was set at 2 mg/dl. A study on 1,234 patients undergoing DES implantation showed that high levels of CRP (>2 mg/dl) were detected in 38% of patients at baseline and in 23.6% during late phase, both stages associated with a higher risk for major cardiac adverse events (MACE). Moreover, high CRP level in the late phase was a better predictor of MACE compared to the CRP level at baseline (14). Our findings are relatively similar with the current literature data. High CRP levels

Table II. Summary table of the specific factors associated with ISR.

Variable	ISR group (n=119) (%)	Non-ISR group (n=116) (%)	P-value
Site of lesion			
LAD	47.9	50.9	NS
RCA	28.6	35.3	NS
LCX	22.7	13.8	NS
LM	0.8	0.0	NS
Clinical diagnosis before stent implantation			
MI right ventricle	0.8	3.4	NS
MI posterior-inferior-lateral	5.0	3.4	NS
MI antero-lateral	8.4	6.9	NS
MI anterior	31.1	29.3	NS
MI inferior	21.0	16.4	NS
Angina pectoris	33.6	40.5	NS
TIMI score			
TIMI 1	2.5	0.0	**0.001**
TIMI 2	19.3	3.4	**0.001**
TIMI 3	78.2	96.6	**0.001**
Ejection fraction (EF)			
EF <40%	52.9	54.3	NS
EF=40-49%	31.9	22.4	NS
EF >50%	15.1	23.3	NS

ISR, intra-stent restenosis; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction; NS, not significant. Significant P-values are presented in bold print.

Table III. Correlation between the type of stent and restenosis.

	Restenosis				
	No restenosis	<1 month	1-12 months	>2 months	Total
Stent type					
DES, N	60	0	13	19	92
% stent type	65.2%	0%	14.1%	20.7%	100%
BMS, N	56	3	39	45	143
% stent type	39.1%	2.1%	27.3%	31.5%	100%
Total					
N	116	3	52	64	235
% stent type	49.4%	1.3%	22.1%	27.2%	100%

DES, drug-eluting stent; BMS, bare-metal stent.

suggest a chronic inflammation that persists even after revascularization.

Another known marker of endothelial dysfunction that registered high levels in our patients with ISR is the uric acid level. Hyperuricemia might inhibit endothelial nitric oxide synthesis and stimulate the secretion of inflammatory cytokines, leading to neointimal hyperplasia associated with a high risk of restenosis (15). The cut-off value for uric acid is different among studies, usually between 6 and 10 mg/dl. A recent analysis of 21,386 individuals identified a prognostic cut-off value of 5.34 mg/dl for all heart failure and 4.89 mg/dl for fatal heart failure (16). Therefore, the values remain debatable. In our study, the cut-off value was established at 5 mg/dl. Even though we observed an increased incidence of elevated uric acid levels in patients with ISR, the correlation was not statistically significant. However, the value of uric acid correlated well with the ISR incidence, in accordance with the literature data (17,18).

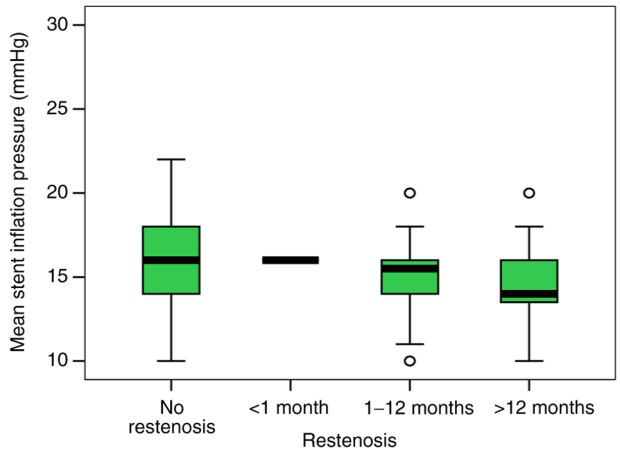

Figure 2. Correlation between mean stent inflation pressure and restenosis.

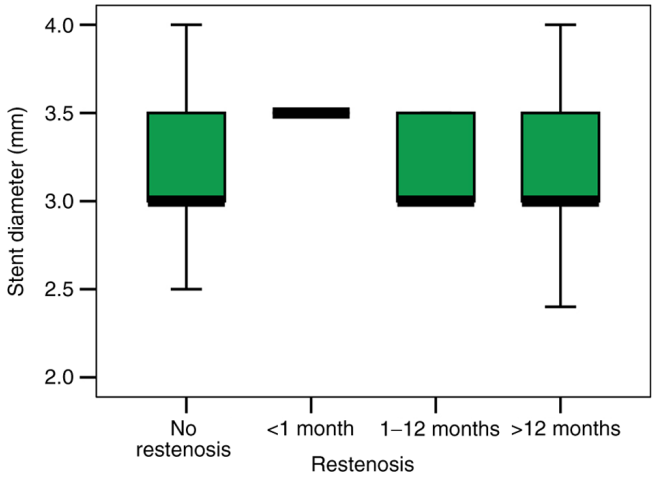

Figure 3. Correlation between stent diameter and restenosis.

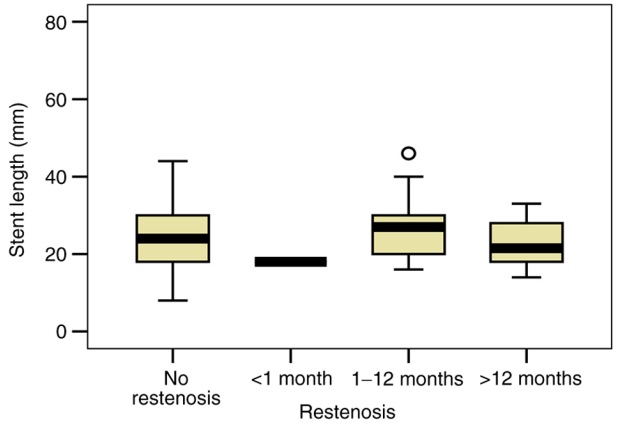

Figure 4. Correlation between stent length and restenosis.

Endothelial dysfunction is also considered a complication in patients with CKD. Modifications at the vascular level influence the evolution after coronary revascularization. Our study defines a statistically significant correlation between CKD and ISR. Data in the literature have also identified a causal relationship between these two variables (19,20).

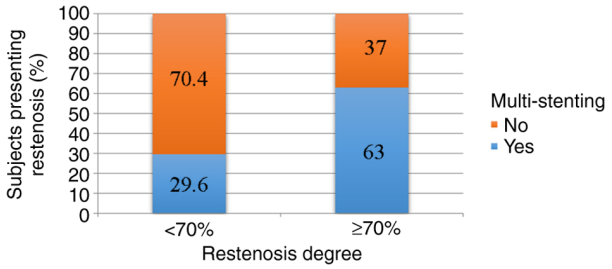

Figure 5. Correlation between multi-stenting and restenosis degree.

Another important factor in the result of the initial procedure and in the evaluation of the risk of unfavorable events in the future is the TIMI score. Results after the initial angiography showed a higher incidence of patients with suboptimal results, especially in patients that presented ISR afterwards (P=0.001). Restenosis at 1-12 months was predominantly represented by patients with TIMI 2 score (52.2%), while restenosis in a period >12 months was predominantly represented by patients with TIMI 3 score (66.7%), but the results were not statistically significant (P=0.184). These results suggest that late restenosis occurs without an association with initial coronarography and initial stent angioplasty.

The advantages of DES over BMS in preventing ISR have been presented in the literature and are also confirmed in our study. Zbinden *et al* showed a significant higher risk of ISR in segments with a BMS compared to segments with a DES (5.4 vs. 0.76% after 2 years) in 2,278 patients (21). In addition, a systematic review concerning the treatment of coronary ISR confirmed a higher rate of ISR after BMS implantation (20-35%) vs. DES implantation (5-10%) (22). In our analysis, BMS presented an associated risk of ISR approximately 2 times higher as compared to DES.

Inflation pressure during stent implantation is correlated to angiographic lumen improvement and stent extension, but the direction of this correlation has not been yet established. In a non-randomized study on 136 patients undergoing PCI with BMS, a high inflation pressure was associated with unfavorable results on long term that included higher rates of MACE and target lesion revascularization (TLR). Higher inflation pressure was associated with an increased risk of ISR and TLR vs. low inflation pressure (71 vs. 16%, respectively 27 vs. 8%) (23). However, in a randomized study, there were no significant differences concerning the risk of ISR when using low or high inflation pressure during stent implementation (24). Another study analyzed moderate to high balloon inflation pressure during PCI and found no measurable improvement in late outcome (25). Finally, a recent retrospective study on over 90,000 stent implementations suggests that a low and a very high pressure elevates the risk of ISR (26). Our results support the findings of this last study. Low pressure was reported in our group of patients with ISR as well as in the group with BMS. Furthermore, our study described a positive correlation between multi-stenting usage and ISR risk. A total of 20.2% of patients from the group with ISR presented 2 or more stents at the region where restenosis was documented vs. 3.4% in the group without ISR (P=0.001).

Our retrospective study has a number of limitations. Firstly, the small sample size analyzed may overestimate the magnitude of an association or even induce false-positive results. The

patients were not divided into ischemic or angina subgroups. However, considering the large amount of data gathered for the analysis, this study also offers an overview of variables that need to be taken into account when establishing correlations with ISR. Secondly, the economical factor has a high influence in the treatment decision of the baseline CAD diagnosis, the study reporting an increased number of BMS implantations.

In conclusion, smoking, hypertension, diabetes mellitus, high CRP levels, CKD, TIMI score, stent type, low pressure for stent implantation and multi-stenting are factors associated with ISR in patients following PCI. Thus, a close follow-up should be targeted in these patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DMA and CAG developed the study concept and design. DMA collected the data and created the database. IIC, LM, AA and CAG performed the literature research and contributed to the introduction, results and discussion sections. OM and IM conducted the statistical analysis and created the images and tables, with assistance from DMA and CAG. All authors were involved in drafting and finalizing the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

The study was approved by the University of Medicine and Pharmacy 'Grigore T. Popa' Iasi Research Ethics Committee and all subjects had initially agreed and signed an informed consent in order to take part in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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