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Factors Associated with Development of in Coronary Stent Restenosis — the Results of a Multislice Computed Tomography 1-year Follow-up Study

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ABSTRACT

Introduction: Percutaneous coronary intervention is the first therapeutic choice in the treatment of symptomatic coronary artery disease and Multi-Slice Computed Tomography Coronary Angiography (MSCT-CA) is a new non-invasive diagnostic tool in the follow-up of these patients. The **aim** of our study was to evaluate the rate of in-stent restenosis (ISR), to identify the predictive factors for ISR at 1 year after PCI and to assess the progression of non-culprit lesions, using a MSCT-CA follow-up. **Material and methods:** The study included 30 patients with acute coronary syndrome treated with one BMS implantation. The patients were divided into Group A (9 patients) presenting ISR and Group B (21 patients) without ISR at 1 year MSCT-CA follow-up. **Results:** ISR lesions were mostly localized on the LAD (45%). No significant difference between the study groups was identified for risk factors, as male gender (77.7% vs. 85.71%, p = 0.62), hypertension (88.8% vs. 95.23%, p = 0.51), smoking status (33.3% vs. 72.22%, p = 0.23), history of CVD (55.5% vs. 47.61%, p >0.99), diabetes (11.11% vs. 19.04%, p >0.99), hyperlipidemia (22.22% vs. 52.38%, p = 0.22), CKD (44.44% vs. 14.28%, p = 0.15), age, triglycerides and SYNTAX Score. A significant difference was recorded in baseline cholesterol level (141.7 ± 8.788 vs. 182.8 ± 12; p = 0.029). Ca Score at 1 year was significantly higher in patients with ISR (603.1 ± 529.3 vs. 259.4 ± 354.6; p = 0.005). 66.67% of patients from Group A presented significant non-culprit lesions at baseline vs. 23.81% in Group B (p = 0.041). **Conclusions:** MSCT-CA is a useful non-invasive diagnostic tool for ISR in the follow-up of patients who underwent primary PCI for an acute coronary syndrome. The presence of significant non-culprit lesions at the time of the primary PCI could be a predictive factor for ISR. A Ca Score >400 determined at 1-year follow-up is associated with a higher rate of ISR, and could be considered a significant cardiovascular risk factor for this group of patients. Further studies are required in order to elucidate the role of various imaging biomarkers in predicting the development of ISR.

Keywords: in-stent restenosis, multislice Angio CT, coronary stent

INTRODUCTION

Percutaneous coronary intervention (PCI) is the first therapeutic choice in the treatment of symptomatic coronary artery disease (CAD), which has become one of the most frequently used procedures in medicine.[1] Even though interventional techniques and materials have evolved in the past decade, restenosis still remains one of the main concerns of an interventional cardiologist. The need of target lesion revascularization (TLR) for restenosis dropped from 30–60% in the plain old balloon angioplasty (POBA) to 16–44% in the bare metal stent (BMS) era, and to only 5–10% in the drug-eluting stent (DES) era, which is still very high considering the number of PCIs performed worldwide.[2]

Neointimal hyperplasia, characterized by the presence of inflammatory cells, extracellular matrix formation, smooth muscle cell (SMC) proliferation and vascular remodeling stays at the basis of in-stent restenosis (ISR).[3,4] ISR was considered a "benign" condition, as it usually does not cause an acute coronary syndrome, but recent studies, using optical coherence tomography (OCT) and intravascular ultrasound (IVUS) have demonstrated that chronic inflammation and endothelial dysfunction lead to *de novo* neoatherosclerotic lesions inside the stented segment after BMS as well as DES implantation, which can ultimately cause an acute coronary syndrome and late stent thrombosis.[5] Some authors even suggest that the magnitude of this phenomenon is as high as one third of the patients with BMS ISR presented MI or unstable angina.[6]

Proper follow-up of patients who underwent PCI is important for an appropriate long-term management, and early detection of significant ISR is key. Several diagnostic methods are available for patients presenting with recurrent angina after PCI, for example stress-ECG, stress-echocardiography, or invasive coronary angiography (ICA). A new non-invasive diagnostic tool in the follow-up of these patients is the Multi-Slice Computed Tomography Coronary Angiography (MSCT-CA), which provides a precise anatomical and quantitative analysis of the ISR lesions. Recent studies have proved the reliance of this technique and demonstrated its high sensitivity, specificity, negative predictive value, representing an important help in the clinical decision-making, and can even lead to the reduction of TLR, compared to ICA.[7,8]

The aim of our study was to evaluate the rate of ISR lesions and to find predictive risk factors for ISR at 1-year follow-up after PCI, and to assess the progression of non-culprit lesions.

MATERIAL AND METHODS

This retrospective study included 30 patients stented for acute coronary syndrome between 2013–2014. The coronary angiography was evaluated, with the identification of the culprit lesion for which primary PCI was done with the implantation of one BMS, with optimal post procedure TIMI III flow.

Other than non-culprit lesions were identified and quantified. A stenosis greater than 50% was considered significant for the Left Main (LM) and proximal Left Anterior Descending artery (LAD), and a stenosis greater than 70% for the rest of the segments. The SYNTAX Score was calculated for all patients. The following risk factors for CAD were analyzed: hypertension, diabetes, history of cardiovascular diseases (CVD), chronic kidney diseases (CKD), smoking (past or present) and hyperlipidemia.

All patients received optimal long-term treatment after discharge, with dual antiplatelet therapy, ACE inhibitors, cardioselective beta-blockers and statins in optimally adjusted doses.

One-year clinical and imagistic follow-up was done with angio-CT, for patients with recurrent angina. All CT acquisitions were made using a Multi-slice 64 Somatom Sensation CT (Siemens, Erlangen, Germany) with dynamic administration (5 ml/s) of 100 ml of contrast material (Iopamiro 370), followed by the administration of 100 ml saline by the right antecubital vein. All examinations were made at a heart rate below 70 bpm, in case of tachycardia beta-blocker (metoprolol) was administrated. No complications appeared during the acquisitions. The obtained images were transferred to a workstation (Siemens, Erlangen, Germany) for data processing, measurements, quantitative and qualitative analysis. Stent patency was assessed, other significant lesions were identified and Ca Score was calculated. A Ca Score greater than 400 was considered as high cardiovascular risk.

The patients were divided into two groups. Group A (n = 9, 30%), with ISR, and Group B (n = 21, 70%), without ISR. A restenosis greater than 50% inside the stented segment, detected by the Multi-Slice Computer Tomography Coronary Angiography (MSCT-CA) was considered significant.

The study has been carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki. All patients gave written informed consent, and the study protocol was approved by the ethics committee of the Cardio Med Medical Center, the center where the study was conducted.

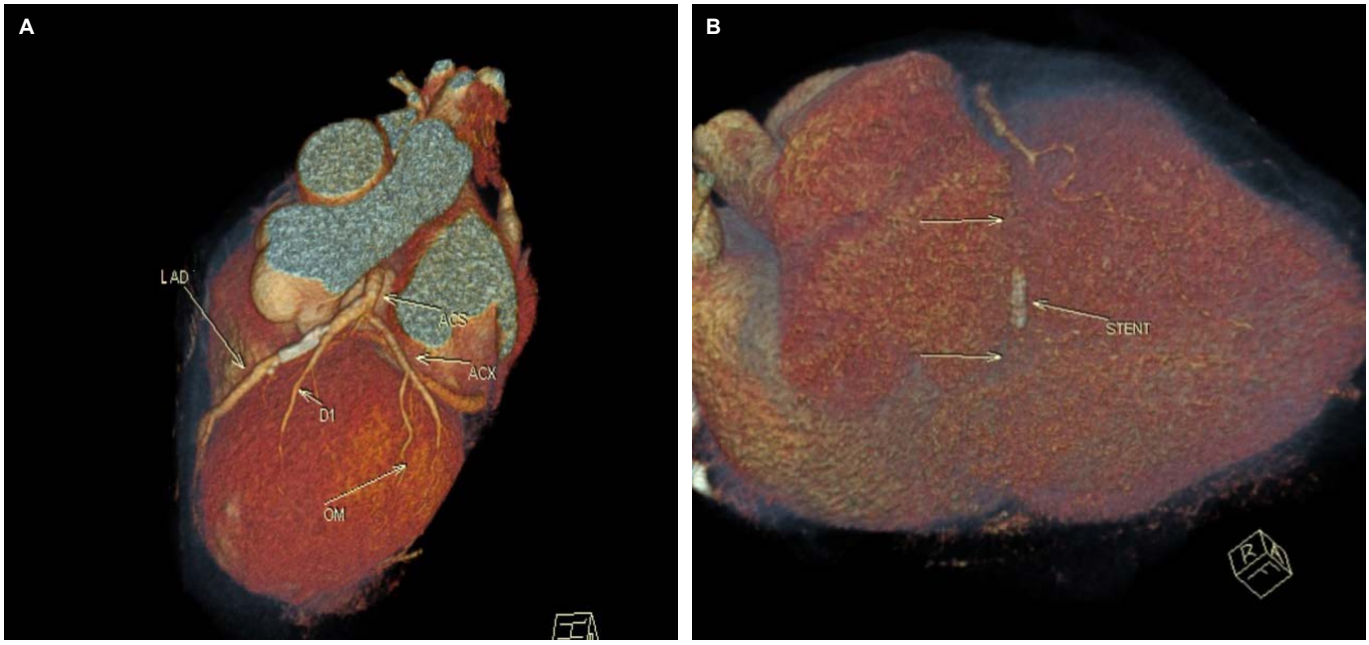

FIGURE 1. **A** – Permeable stent in segment II of the LAD. **B** – RCA occlusion proximally from the implanted stent

STATISTICAL ANALYSIS

Graph Pad Prism 7.0 software was used for statistical analysis. Mann-Whitney test was used for continuous values that are expressed as means ± SD. Fisher's exact test was used for the comparison of categorical variables expressed as percentages. The level of significance was set at $\alpha = 0.05$.

RESULTS

A total number of 30 implanted BMSs were analyzed using 1-year MSCT-CA follow-up. Most stents were localized on the LAD (n = 18, 60%), followed by an equal number (n = 6, 20%) on the Circumflex Artery (CX) and the Right Coronary Artery (RCA).

Figure 1 represents an exemplification of two stents: one patent stent, implanted in the LAD (Figure 1A) and one occluded, implanted in the RCA (Figure 1B). The proximal and mid segment of each artery were the most affected segments (Figure 2).

Other significant non-culprit lesions were identified and localized from the baseline coronary angiography (n = 18). The LAD was the most affected vessel, accounting for 50% (n = 9) of these lesions, followed by the CX (n = 6, 33.33%) and the RCA (n = 3, 16.66%).

ISR was determined and localized at the 1-year MSCT-CA follow-up. Nine ISR lesions were identified, mostly localized on the LAD (45%) and the CX (33%) (Figure 3).

There was no significant difference between the two groups in terms of risk factors, such as male gender (p =

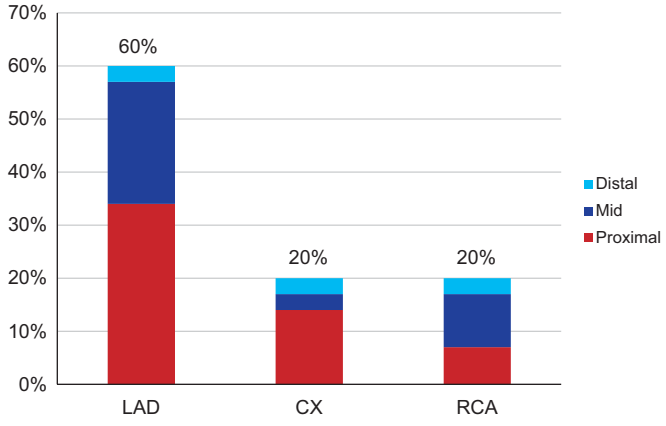

FIGURE 2. Localization of the implanted stents

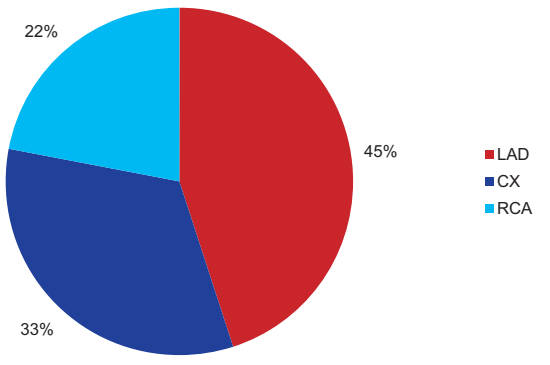

FIGURE 3. Localization of the ISR lesions

TABLE 1. Risk factors in the study population

	Group A With ISR n = 9 (30%)	Group B Without ISR n = 21 (70%)	p value
Gender, Male	7 (77.7%)	18 (85.71%)	0.62
Hypertension	8 (88.8%)	20 (95.23%)	0.51
Smoker	3 (33.3%)	13 (72.22%)	0.23
CVD history	5 (55.5%)	10 (47.61%)	1
Diabetes	1 (11.11%)	4 (19.04%)	1
Hyperlipidemia	2 (22.22%)	11 (52.38%)	0.22
CKD	4 (44.44%)	3 (14.28%)	0.15

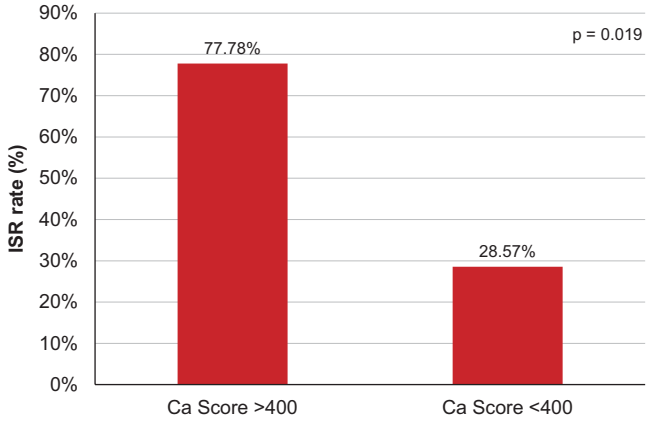

FIGURE 4. Correlation between the high Ca Score and the presence of ISR

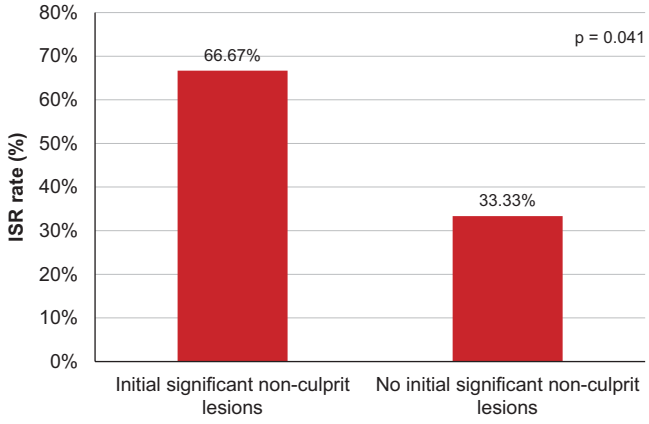

FIGURE 5. Significant non-culprit lesions and ISR

0.62), hypertension (p = 0.51), smoking status (p = 0.23), history of CVD (p = 1), diabetes (p = 1), hyperlipidemia (p = 0.22) and CKD (p = 0.15) (Table 1).

The clinical baseline characteristics of the patients show significant differences in respect to the cholesterol level (p = 0.029), however the differences were not significant regarding age (p = 0.3), triglycerides (p = 0.9) and the SYNTAX score (p = 0.2) (Table 2).

The Ca Score at 1 year postintervention was significantly higher in patients who developed ISR (603.1 ± 529.3 vs. 259.4 ± 354.6; p = 0.005). A Ca Score >400 was detected in 77.78% of patients in Group A compared to only 22.22% of patients in group B (p = 0.019, OR = 8.75, 95% CI = 1.454–46.92) (Figure 4).

Patients with significant non-culprit lesions described at the primary coronary angiography presented a more pronounced progression of the atherosclerotic process at the 1-year follow-up compared to patients without other significant lesions, as demonstrated by the presence of non-culprit lesions at baseline in 66.67% of patients from Group A compared to only 23.81% in Group B (p = 0.0419, OR: 0.156, 95% CI = 0.035–0.883) (Figure 5).

DISCUSSIONS

The aim of our study was to determine the rate and predictive factors of ISR in 30 patients with one implanted BMS for an acute coronary syndrome and 1-year MSCT-CA follow-up. We have analyzed the presence of hypertension, diabetes mellitus, CKD, history of CVD, the smoking status and the hyperlipidemia, without identifying any significant difference between the groups in respect to risk factors, despite the fact that various studies have demonstrated that diabetes mellitus is an important predictive factor.[9] This might indicate that the development of ISR

TABLE 2. Baseline characteristics of the study population

	Group A With ISR		Group B Without ISR		p value
	Mean + SD	95% CI	Mean +SD	95% CI	
Age	59.05 ± 2.474	55.01–71.44	63.22 ± 3.562	53.89–64.21	0.355
Cholesterol	141.7 ± 8.788	121.7–162.7	182.8 ± 12	157.3–208.2	0.029
Triglycerides	112.6 ± 8.717	92.02–133.3	113.9 ± 10.85	90.74–137	0.941
SYNTAX Score	12.67 ± 1.434	9.36–15.97	10.14 ± 1.24	7.55–12.73	0.244

may be related to other risk factors for atherosclerosis, along the ones already well-known.

Another observation in our study was the high rate of restenosis with LAD localization. The path of the artery, multiple branches with higher shear stress and smooth muscle cell proliferation could explain the more frequent localization at this level.[10]

The Coronary Calcium Score determined with MSCT is a widely accepted cardiovascular risk factor and a Coronary Calcium Score >400 is considered to be high risk for CVD.[11] A significantly higher rate of >400 Ca Score was determined in patients with ISR, meaning that Ca Score could be a predictor for ISR too.

Even though the natural course of the atherosclerotic process can be slowed down, and the reduction of cardiovascular risk can be attainted with optimal statin therapy, atherosclerosis remains a dynamic, progressive disease.[12] Neointimal proliferation is considered to represent a key physiopathologic pathway for ISR, however the role of the atherosclerotic lesion progression and the appearance of neoatherosclerotic plaques has to be considered, as a higher ISR rate was observed in patients which presented significant non-culprit lesions at the baseline coronary angiography.[13] The detection of these plaques is extremely important as they can be unstable, vulnerable lesions and ultimately cause an acute coronary syndrome. MSCT has already proved its liability in the detection of unstable plaques in native coronary arteries, however qualitative analysis of the ISR plaques was beyond the scope of our study, and further studies are required to determine the role of MSCT in assessment of vulnerable plaques in ISR.[14,15]

CONCLUSIONS

MSCT-CA is a useful non-invasive diagnostic tool for ISR in the follow-up of patients who underwent primary PCI for an acute coronary syndrome. The presence of significant non-culprit lesions at the time of the primary PCI could be a predictive factor for ISR. A >400 Ca Score determined at 1-year follow-up is associated with a higher rate of ISR, and could represent a cardiovascular risk factor for this group of patients.

STUDY LIMITATIONS

A small number of patients were included in this study, therefore the conclusions cannot be generalized. Further studies are required, with complex qualitative plaque analysis of the ISR lesions, in order to elucidate the role of various imaging biomarkers in predicting the development of ISR.

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CONFLICT OF INTEREST

Nothing to declare.

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