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Predictors of Diffuse In–Stent Restenosis, a Retrospective Analysis in a Subset of Egyptian Population.

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Abstract

Background: Despite the fact that DES implantation has decreased the incidence of ISR dramatically, it is not negligible. Diffuse ISR is associated with poor outcomes. Most of the data regarding ISR are obtained from studies including BMS stents.

Methods: A total of 263 ISR patients were treated at two tertiary care hospitals from September 2017 through December 2022. 40 patients were excluded because the previous angiography and procedure details were not available, IVUS data were available for only 30 patients and the patients were not included in the analysis, so only 193 ISR patients were included in the analysis. We compared different clinical and procedural risk factors between diffuse and focal patterns of ISR following DES implantations.

Results: A total of 193 ISR lesions were included in the analysis, distributed as 53.4% diffuse pattern and 46.6% focal pattern. In the multivariate analysis, only increased stent length [OR 1.270 (1.157 – 1.394) 95%CI, P<0.001], lower LVEF [OR 0.903, (0.860 – 0.949) 95%CI, P<0.001], occurrence of procedural complications [OR 15.584 (2.075 – 117.044) 95%CI, P=0.008], smoking [OR 3.182, (1.071 – 9.451) 95%CI, P=0.037] and older age [OR 1.086, (1.014 – 1.163) 95%CI, P=0.019] were independent risk factors of diffuse ISR. DM was not associated with diffuse ISR in the multivariate analysis.

Conclusions: Increased age, smoking, reduced left ventricular ejection fraction, occurrence of procedural complications and increased stent length are independent predictors of diffuse ISR. Diabetes mellitus was not found to be independently associated with a diffuse pattern of ISR.

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Keywords: *Diffuse in-stent restenosis, stent length, predictors of in-stent restenosis.*

Introduction

Coronary artery disease (CAD) was responsible for 382.820 deaths in 2020 and it affects about 20.1 million adults aged 20 and older who have CAD.[1] Currently, percutaneous coronary intervention (PCI) is the main treatment for CAD cases, especially in acute coronary syndromes (ACS). This is because PCI improves myocardial ischemia and protects against adverse vascular events in ACS patients.[2] Approximately 60% of ACS cases receive invasive management and stent implantation, and this number is increasing annually.[3,4] However, despite the advances in stent manufacturing and pharmacological therapies, in-stent restenosis (ISR) remains a major challenge and is associated with significant morbidity.[5,6] ISR increases the incidence of major adverse cardiovascular events (MACEs).[7]

ISR occurred in 20–35% after bare-metal stents (BMS). Although the introduction of drug-eluting stents (DES) reduced the risk of ISR significantly, ISR still occurs in 5–10% of patients.[8]

The use of intravascular imaging, i.e., intravascular ultrasound (IVUS) and optical coherence tomography (OCT), has emerged for a better understanding of ISR pathophysiology and mechanisms, but these interventions are invasive, expensive, and not readily available in all centers.[9] Mahran et al, developed an angiographic classification of ISR according to the distribution of intimal hyperplasia in reference to the implanted stent. They also found the higher the class of ISR, the higher the risk of target lesion revascularization (TLR).[5]

Diffuse patterns of ISR have also been associated with a higher rate of recurrent restenosis and poor prognosis than focal pattern ISR.[10] Therefore, the present study sought to identify the predictors of diffuse-type ISR following successful DES implantation.

Regarding the management of ISR, current ESC guidelines recommend the use of either DESs or DCBs with consideration for intracoronary imaging to treat ISR.[11] DCBs have been recently approved for the management of ISR in the United States. ACC guidelines recommend that patients who develop ISR after DES implantation may be considered for repeat percutaneous coronary intervention with DESs containing the same antiproliferative drug or an alternative antiproliferative drug if coronary anatomic factors are appropriate and the patient is able to comply with and tolerate dual antiplatelet therapy. Additionally, these guidelines suggest that intravascular ultrasound is reasonable to determine the mechanism of ISR.[12]

Methods

Patient Population

A total of 263 ISR patients were treated at tertiary care hospital from September 2017 through November 2022. We excluded 40 patients because the previous angiography and procedure details were not available, IVUS data were available for only 30 patients and were not included in the analysis. So only 193 ISR patients were included in the analysis for the predictors of late-onset ISR, with follow-up period of at least one year.
The hospital records were reviewed to obtain clinical and demographic data of the enrolled patients. Coronary angiograms -of both the initial procedure and the ISR procedure- were analyzed by two experienced investigators who were not aware of the purpose of the study. The reference vessel diameter, the percent diameter stenosis and the minimal luminal diameter were determined using quantitative coronary angiography (QCA) (Xelera Cath 1.1, Philips). The angiographic measurement was made during the end-diastole following intracoronary nitroglycerin administration, and lesions were classified according to Mehran classification. Procedural complications were also analyzed and were defined as the occurrence of inlet or outlet dissection, distal vessel dissection, side branch occlusion, stent thrombosis, no-reflow or cardiac death.

Statistical analysis of the data:

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to compare between two groups. Alternatively, Fisher Exact or Monte Carlo correction test was applied when more than 20% of the cells had expected count of less than 5. For continuous data, they were tested for normality by the Kolmogorov- Smirnov test. Quantitative data were expressed as a range (minimum and maximum), mean, standard deviation and median

Table 1. Distribution of the studied cases according to type of ISR (n = 193).

Type of ISR	No. (%)
Non-focal	103 (53.4%)
Diffuse intrastent	27 (14.0%)
Diffuse proliferative	30 (15.5%)
Occlusive	46 (23.8%)
Focal	90 (46.6%)
Inlet	7 (3.6%)
Mid	72 (37.3%)
Outlet	5 (2.6%)
Multifocal	6 (3.1%)

Table 2. Distribution of the studied cases according to Mehran Classification (n = 193).

Mehran Classification	No. (%)
Non-focal /diffuse	
IV	46 (44.7%)
II	27 (26.2%)
III	30 (29.1%)
Focal	
IB	12 (13.3%)
IC	72 (80.0%)
ID	6 (6.7%)

for normally distributed quantitative variables Student t-test was used to compare two groups. On the other hand, for not normally distributed quantitative variables Mann Whitney test was used to compare two groups. Logistic regression analysis was used to detect the most independent factor for affecting diffuse ISR. The significance of the obtained results was judged at the 5% level.

Results

A total of 193 ISR lesions were included in the analysis, distributed as 53.4% diffuse pattern and 46.6% focal pattern as shown in **tables 1, 2.**

Among these 193 ISR patients, the mean age was 61.4 years with males representing 66.8%, hypertension was present in 54.9%, diabetics represented 64.8%, uncontrolled diabetics (defined as HbA1C more than 7%) represented 65.6% of the diabetic patients, 88.6% of these patients had a previous history of ACS as presenting symptoms.

Different demographic, clinical, and procedural data are presented in **tables 3,4.**

The diffuse ISR group was significantly older. Hypertension, diabetes mellitus (DM), uncontrolled DM, and smoking were significantly higher in diffuse ISR patterns. No significant difference between both groups (focal or diffuse ISR) regarding LDL-cholesterol levels. Regarding the left ventricular systolic function, the diffuse ISR group had a significantly lower mean LVEF than the focal ISR group.

Comparing the two groups according to PCI procedure data, we found that diffuse ISR patients had significantly higher number of stents per patient than focal ISR (1.66 ± 0.62 vs 1.51 ± 0.69, respectively, P= 0.044). Also, longer stents were seen in the diffuse group compared to a focal pattern (32.6 ± 5.73 mm vs 24.7 ± 5.82 mm, respectively, P<0.001). The diffuse ISR patient showed also more tight lesions at baseline

Table 3. Comparison between diffuse and focal ISR according to demographic and clinical characteristics.

	Total (n = 193)	Diffuse (n = 103)	Focal (n = 90)	P
Age (years)				
Mean ± SD.	61.4 ± 7.61	62.6 ± 7.30	60 ± 7.76	0.019*
Median (Min. – Max.)	62 (38 – 78)	63 (43 – 78)	61 (38 – 76)	
Gender				
Male	129 (66.8%)	73 (70.9%)	56 (62.2%)	0.203
Female	64 (33.2%)	30 (29.1%)	34 (37.8%)	
HTN	106 (54.9%)	65 (63.1%)	41 (45.6%)	0.014*
DM				
Non diabetics	68 (35.2%)	23 (22.3%)	45 (50.0%)	<0.001*
Insulin requiring DM	61 (31.6%)	40 (38.8%)	21 (23.3%)	0.021*
DM on OHD	64 (33.2%)	40 (38.8%)	24 (26.7%)	0.073
Controlled DM	(n = 125)	(n = 80)	(n = 45)	
No (HbA1C >7)	82 (65.6%)	65 (81.3%)	17 (37.8%)	<0.001*
Yes (HbA1C <7)	43 (34.4%)	15 (18.8%)	28 (62.2%)	
History of A.C.S.	171 (88.6%)	92 (89.3%)	79 (87.8%)	0.737
Smoking	138 (71.5%)	86 (83.5%)	52 (57.8%)	<0.001*
Dyslipidemia	154 (79.8%)	86 (83.5%)	68 (75.6%)	0.171
LDL (mg/dl)	41.62±15.85	43.06±17.12	41.44±15.67	0.26
FH CAD	30 (15.5%)	13 (12.6%)	17 (18.9%)	0.231
History of CABG	14 (7.3%)	5 (4.9%)	9 (10.0%)	0.169
Compliance to dual antiplatelet therapy	167 (86.5%)	87 (84.5%)	80 (88.9%)	0.369
EF (%)				
Mean ± SD.	55.7 ± 13.6	48.3 ± 11.6	64.1 ± 10.4	<0.001*
Median (Min. – Max.)	55 (23 – 78)	48 (23 – 73)	65 (35 – 78)	

SD: Standard deviation

p: p value for comparing between diffuse ISR and Focal ISR

*: Statistically significant at $p \leq 0.05$

as assessed by QCA, mean diameter stenosis percentage was significantly higher compared to focal ISR (89.98 ± 12.8% vs 84.1 ± 16.4%, respectively, P<0.001). Evidence of disease progression to other vessels was noted more significantly in the diffuse group representing 61.2% compared to only 41.1% in the focal group, P=0.005. LAD lesions and side branch occlusions were also more significant in the diffuse ISR group (P=0.005, 0.004 respectively).

Using logistic regression analysis for identification of factors affecting diffuse ISR, in the univariate analysis we found that advanced age, presence of hypertension, DM, smoking, LAD lesions, lower LVEF, occurrence of procedural complications (i.e., dissection and side branch loss), disease progression into other vessels and stent length are the factors associated with diffuse ISR.

In the multivariate analysis, only increased stent length [OR 1.270 (1.157 – 1.394) 95%CI, P<0.001], lower LVEF [OR 0.903, (0.860 – 0.949) 95%CI, P<0.001], occurrence of procedural complications [OR 15.584 (2.075 – 117.044) 95%CI, P=0.008], smoking [OR 3.182, (1.071 – 9.451) 95%CI, P=0.037] and older age [OR 1.086, (1.014 – 1.163) 95%CI, P=0.019] are independent risk factors of diffuse ISR. **Table 5**.

Table 4. Comparison between diffuse and focal ISR according to procedural data.

	Total (n = 193)	Diffuse (n = 103)	Focal (n = 90)	P
Total no. of stents				
Mean ± SD.	1.59 ± 0.66	1.66 ± 0.62	1.51 ± 0.69	0.044*
Median (Min. – Max.)	2 (1 – 4)	2 (1 – 4)	1 (1 – 3)	
Calcification	18 (9.3%)	10 (9.7%)	8 (8.9%)	0.845
Bifurcation lesion	5 (2.6%)	2 (1.9%)	3 (3.3%)	FEp=0.666
Vessel affected				
LAD	127 (65.8%)	77 (74.8%)	50 (55.6%)	0.005*
LCX	21 (10.9%)	9 (8.7%)	12 (13.3%)	0.306
RCA	35 (18.1%)	14 (13.6%)	21 (23.3%)	0.080
LM	10 (5.2%)	3 (2.9%)	7 (7.8%)	FEp=0.193
Pre-dilation	134 (69.4%)	70 (68.0%)	64 (71.1%)	0.636
Post dilation	124 (64.2%)	67 (65.0%)	57 (63.3%)	0.804
Type of drug eluted				
EES	131 (67.9%)	73 (70.9%)	58 (64.4%)	
PES	27 (14.0%)	17 (16.5%)	10 (11.1%)	MCp=0.160
SES	25 (13.0%)	11 (10.7%)	14 (15.6%)	
BES	4 (2.1%)	1 (1.0%)	3 (3.3%)	
NES	6 (3.1%)	1 (1.0%)	5 (5.6%)	
Stent diameter				
Mean ± SD.	3.07 ± 0.43	3.02 ± 0.42	3.13 ± 0.43	0.089
Median (Min. – Max.)	3 (2.25 – 4)	3 (2.25 – 4)	3 (2.50 – 4)	
Stent length				
Mean ± SD.	28.9 ± 6.97	32.6 ± 5.73	24.7 ± 5.82	<0.001*
Median (Min. – Max.)	28 (10 – 48)	32 (18 – 48)	28 (10 – 36)	
Overlapping stents	6 (3.1%)	4 (3.9%)	2 (2.2%)	FEp=0.687
Occurrence of Procedural complication				
No complication	176 (91.2%)	88 (85.4%)	88 (97.8%)	0.003*
Dissection	1 (0.5%)	1 (1.0%)	0 (0.0%)	FEp=1.000
Side branch occlusion	16 (8.3%)	14 (13.6%)	2 (2.2%)	0.004*
Duration between stent insertion and Restenosis (/ months)				
Mean ± SD.	37 ± 27.1	34 ± 24.7	40.5 ± 29.3	0.091
Median (Min. – Max.)	33 (1 – 83)	32 (1 – 82)	47 (1 – 83)	
Stent deployment				
Optimal	156 (80.8%)	78 (75.7%)	78 (86.7%)	0.054
Under-deployment	37 (19.2%)	25 (24.3%)	12 (13.3%)	
Disease progression to other vessels	100 (51.8%)	63 (61.2%)	37 (41.1%)	0.005*
Diameter stenosis (%)				
Mean ± SD.	87.2 ± 14.8	89.98 ± 12.8	84.1 ± 16.4	<0.001*
Median (Min. – Max.)	95 (50 – 100)	99 (60 – 100)	90 (50 – 99)	

SD: Standard deviation, p: p value for comparing between diffuse ISR and Focal ISR, *: Statistically significant at $p \leq 0.05$

Table 5. Univariate and multivariate logistic regression analysis for the parameters affecting diffuse ISR (n = 103 vs. 90) .

	Univariate		#Multivariate	
	P	**OR (LL – UL 95%C.I)**	**P**	**OR (LL – UL 95%C.I)**
Age (years)	0.021*	1.047 (1.007 – 1.088)	0.019*	1.086 (1.014 – 1.163)
History of HTN	0.015*	2.044 (1.149 – 3.638)	0.182	1.998 (0.723 – 5.520)
Presence of DM	<0.001*	3.478 (1.869 – 6.473)	0.275	1.788 (0.631 – 5.071)
Smoking	<0.001*	3.697 (1.896 – 7.207)	0.037*	3.182 (1.071 – 9.451)
EF (%)	<0.001*	0.881 (0.849 – 0.914)	<0.001*	0.903 (0.860 – 0.949)
Total no. of stents	0.117	1.426 (0.915 – 2.221)		
Presence of LAD lesion	0.005*	2.369 (1.289 – 4.355)	0.099	2.448 (0.845 – 7.089)
Occurrence of Procedural complication	0.009*	7.500 (1.666 – 33.771)	0.008*	15.584 (2.075 – 117.044)
Presence of Disease progression to other vessels	0.006*	2.256 (1.267 – 4.019)	0.208	2.137 (0.655 – 6.971)
Stent under-deployment	0.057	2.083 (0.978 – 4.439)		
Stent Diameter	0.058	0.519 (0.263 – 1.024)		
Stent Length	<0.001*	1.300 (1.200 – 1.407)	<0.001*	1.270 (1.157 – 1.394)

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate , *: Statistically significant at p ≤ 0.05

Discussion

Despite the fact that DES implantation has decreased the incidence of ISR dramatically, it is not negligible. Diffuse ISR is associated was poor outcomes. [10] Most of the data regarding ISR are obtained from BMS stents. In the current study, we compared different clinical and procedural risk factors between diffuse and focal patterns of late-onset ISR with DES, which may be helpful for the prevention of this type and the prevention of future events.

Our main findings, that patients with advanced age, smoking, reduced LV ejection fraction, procedural complications, and longer stents are more prone to diffuse type of ISR. Another important finding was that in the multivariate analysis, DM was not an independent risk factor of diffuse ISR.

On the basis of the results, we identified older age as a predictor of diffuse ISR by logistic regression analysis (OR 1.086, (1.014 – 1.163) 95%CI, P=0.019). In line with our data, several previous trials reported advanced age as a risk factor of ISR but did not correlate age with ISR subtypes.[13-15] Elderly patients with multiple comorbidities consistently exhibit increased arterial wall thickness and stiffness which may explain the increased risk of diffuse nature of restenosis.

Plaque rupture and subsequent inflammatory response lead to angiographic stenotic progression. Smokers have more rupture-prone unstable plaques than non-smokers.[16] Therefore, smoking may contribute to a more complex ISR pattern. Although published studies have reported conflicting data regarding the association between smoking and ISR[15,17-19], our results suggested that smoking after DES implantation served as a risk factor for a more advanced pattern of ISR.

In a recent study, Li et al, found that reduced LVEF and increased stent numbers were the only independent risk factors of ISR in the Chinese population.[20] We also found in the multivariate analysis that reduced LVEF is an independent risk factor of diffuse ISR. Patients with reduced LV function may have reduced systolic and diastolic blood pressure, which may predispose to reduced coronary perfusion, also these patients may have more prevalent cardiovascular comorbidities and risk factors which may cause more extensive CAD with longer lesion length which may need long or overlapping stents for treatment. Usage of long stents may predispose more to ISR.

Interestingly we found the occurrence of procedural complications is an independent factor of diffuse ISR. This may be explained by the probability of subacute results and presence of slow flow and thrombosis in case of procedural complication that may invite more progressive nature of ISR. We also found a wide gap

in the confidence interval in the multivariate analysis, which may be related to the small size of the study population, which is one of our study limitations.

Studies have suggested increased stent length as a risk factor of ISR. In our study, we found that stent length is an independent predictor of diffuse ISR. A study done by Hong and his colleagues found that stent length (>40 mm) was an independent predictor of ISR development.[21] Another study investigated the predictors of diffuse and aggressive in-stent restenosis and found that longer lesions and longer stent length were associated with more aggressive ISR.[22]

Diabetes mellitus (DM), is generally considered an established risk factor for ISR.[23] It has been reported that controlled DM with HbA1c<7.0% is associated with a reduced risk of restenosis and repeat revascularization. [24] It was also noted that intense glycemic control improves the cardiovascular outcome after ACS among both diabetic and non-diabetic hyperglycemic subjects.[25,26] On the contrary, in the current study we found DM was not associated with diffuse ISR in the multivariate logistic regression analysis. Our finding is in line with Zheng et al, who found that DM was not associated with ISR.[15] Also Park et al, found that DM was not a predictor of a diffuse pattern of ISR as observed in our study.[27] Another study showed that DM was associated with stent edge restenosis rather than diffuse or other subtypes of ISR.[14]

Study limitations:

Our study is limited because it is a single-center study, lacking intravascular imaging (IVUS or OCT), and limited by the small sample size.

Conclusions

Increased age, smoking, reduced left ventricular ejection fraction, occurrence of procedural complications and increased stent length are independent predictors of diffuse ISR. Diabetes mellitus was not found to be independently associated with diffuse pattern of ISR.

List of abbreviations

ACS	Acute Coronary Syndromes
BMS	Bare Metal Stents
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
DES	Drug Eluting Stents
DM	Diabetes Mellitus
FH	Family History
HTN	Hypertension
ISR	Instent Restenosis
IVUS	Intravascular Ultrasound
LDL-C	Low Density Lipoprotein Cholesterol
LVEF	Left Ventricle Ejection Fraction
MACE	Major Adverse Cardiovascular Events
OCT	Optical Coherence Tomography

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