

The Clinical Spectrum and Management of Patients with Coronary In-Stent Restenosis

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Abstract

Background: In-stent restenosis (ISR) is a common clinical problem that continues to be one of the most important limitations of percutaneous coronary intervention (PCI). It is associated with significant morbidity and costs, and is not a benign entity, with a wide spectrum of clinical presentation.

Aim of Study: To detect the prevalence of ISR in a tertiary referral center carried out for patients presented to AL-Nahda General Hospital at Taif, Kingdom of Saudi Arabia and underwent clinically driven coronary angiography with a history of previous PCI. Those with missed procedural data related to the previous PCI were excluded from the study.

Material and Methods: This was a retrospective- prospective study carried out on patients presented to AL-Nahda General Hospitals from November 2018 to November 2019 (350 patients records as a total coverage, 100 were collected as eligible) who underwent coronary angiography with a history of previous PCI.

Results: Among the studied population, males were 68 (68%) and females were 32 (32%). Mean age was 53 ± 10 . Out of 100 patients, in-stent restenosis (ISR) was documented in fifty (50%) patients (45 males and 5 females) and not documented in fifty (50%) patients (27 males - 23 females). The statistical differences were; male gender [90% versus 46%, respectively; p -value < 0.001], DM (72% versus 38%, respectively; p -value < 0.001), Pre and post stenting balloon dilatation [16% versus 2%, respectively; p -value = 0.031], LAD lesion (52% versus 10%, respectively; p -value = 0.002), pre-stent minimal lumen diameter (MLD) (p -value < 0.01); the stents in the patients with ISR were smaller in diameter and longer in length. The ISR group was then subdivided according to the lesions characters of in-stent restenosis into two groups: Focal group (22 male - 5 female) and non-focal (Diffuse Proliferative) (23 male - 0 female). Diffuse-type ISR was more common in LAD and RCA lesions 78.3% and 56.5% respectively

with (p -values were 0.0001 and 0.028 respectively). During the previous procedure the use of balloon for pre and post stent dilatation was higher in the diffuse-type ISR with statistically significant difference, p -value ≤ 0.010 . The diameter of the stents in ISR patients was small in the diffuse-type ISR (stent diameter was 2.62 ± 0.56 mm in the diffuse-type ISR and 3.04 ± 0.31 mm in the focal group, with statistically significant difference, p -value ≤ 0.002) and the stents length was longer in the diffuse-type ISR (29.35 ± 9.26 mm) versus (22.11 ± 7.91 mm), with statistically significant difference (p -value ≤ 0.005). During the follow up the diffuse type was associated with more complications and one case mortality.

Conclusion: A number of factors have been associated with the propensity to develop stent restenosis, including male gender, diabetes mellitus, LAD lesion, small stent diameter, increased stent length; balloon used pre or post stenting and pre-stenting MLD which were all predictors of restenosis in this study. Diabetes mellitus, stent length and pre stenting minimal lumen diameter (MLD) were independent predictors of ISR. This study also showed that pre-stenting MLD, pre and post stenting balloon dilatation, DM, Male sex, LAD, RCA, and the stent length and diameter are predictors of diffuse (non-focal) type ISR.

Key Words: In-stent restenosis – Stent – Coronary Arteries – RCA – LAD – Angiography.

Introduction

RE-STENOSIS implies reducing diameter of a blood vessel after percutaneous angioplasty [1]. In-stent restenosis (ISR) is a challenging medical dilemma [2]. A meta-analysis revealed that percutaneous coronary intervention (PCI) for ISR is accompanied with a higher occurrence of adverse cardiac events than PCI for de novo lesions [3]. Even though it is a lesser faced problem than before due to use of new generation drug-eluting stents, it remains to play a major role in modern medical practice since extensive number of stents are inserted in current practice [4].

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Aim of the work:

Primary objective: To detect the Prevalence of ISR in a tertiary referral center.

Secondary objectives: To identify the clinical and procedural predictors of angiographic ISR in the modern era and to explore clinical and angiographic factors determining management in a tertiary referral center.

Patients and Methods

This was a retrospective-prospective study carried out on 100 patients reporting to Al-Nahda General Hospitals from November 2018 to November 2019 (350 patients records as a total coverage from them 100 were collected as eligible) who underwent clinically driven coronary angiography with a history of previous PCI. Those with missed procedural data related to the previous PCI were excluded from the study. All the included population underwent the following diagnostic work-up after taken a written consent from each one: Clinical evaluation (including age, gender, cardiovascular risk factors, clinical presentation), procedural data related to the previous PCI, laboratory data (including serum creatinine, creatinine clearance, cardiac enzymes and Lipid profile), 12-lead ECG, and transthoracic echocardiography for evaluation of cardiac function and wall motion abnormalities, finally coronary angiography with qualitative coronary angiography analysis (QCA) for assessment of stented segment, management according to their presentations then follow-up for 6 months.

Statistical analysis: Was done and data were expressed as the mean \pm SD for continuous variables and frequencies for categorical variables. Continuous variables were compared by unpaired Student's *t*-test and categorical variables by Chi-square test. A *p*-value of <0.05 was considered as statistically significance. The ethical issues were approved from ethical committee.

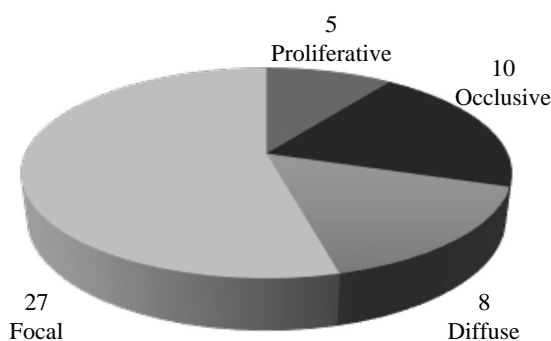
Results

All the patients underwent coronary angiography which showed in-stent restenosis lesions in Fifty (50%) of the patients (45 male - 5 female) with focal type ISR developed in 27 lesions (16 edge and 11 bodies), and non-focal-type ISR in 23 lesions (10 occlusive, 8 diffuse, 5 proliferative) and patent stents in (27 male - 23 female). Patients were divided according to the presence of in-stent restenosis (ISR) into two groups: patients with and without ISR. The statistical differences were; Male sex [90% versus 46%, respectively; *p*-value <0.001], DM (72% versus 38%, respectively; *p*-value <0.001), Pre and Post stent balloon dilatation [16% versus 2%, respectively; *p*-value <0.031], LAD lesion (52% versus 10%, respectively; *p*-value <0.002) and pre stent minimal lumen diam-

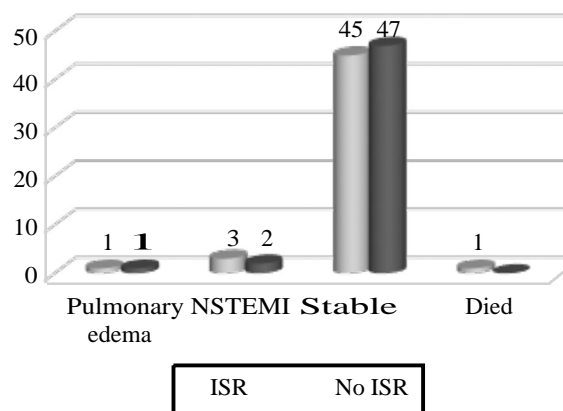
eter (MLD) (*p*-value <0.0001). The stents in the patients with ISR were smaller in diameter and its length was longer. (Tables 1,2).

The ISR group was then subdivided according to the lesions characters of in-stent restenosis (ISR) into two groups: Focal group (22 male - 5 female) and non-focal (Diffuse Proliferative) (23 male - 0 female). Diffuse-type ISR was more common in LAD and RCA lesions 78.3% and 56.5% respectively with (*p*-values were 0.0001 and 0.028 respectively). During the previous procedure the use of balloon for pre and post stent dilatation was higher in the diffuse-type ISR with statically significance *p*-value ≤ 0.001 . The diameter of stents in ISR patients was small, (stent diameter was 2.62 ± 0.56 mm in the diffuse-type ISR and 3.04 ± 0.31 mm in the focal group, with statically significance *p*-value ≤ 0.002) and the Stents length was longer (29.35 ± 9.26 mm) versus (22.11 ± 7.91 mm), with statically significance (*p*-value ≤ 0.005). (Tables 3,4).

During the follow-up the diffuse type is associated with more complications as In-stent restenosis (ISR) group those patients had higher rate of acute coronary syndrome (NSTEMI), higher rate of chronic stable angina and one case mortality as in Graph (2).



Graph (1): In-stent restenosis lesions characters according classification to Mehran.



Graph (2): The follow-up (6M) outcomes differences between the ISR and no ISR.

Table (1): The previous procedural data differences between the ISR and no ISR.

Variables	ISR (n = 50)	No ISR (n = 50)	p-value
Residual stenosis	3 (6%)	0 (0%)	0.242
Dissection	2 (4%)	1 (2%)	1
<i>TIMI:</i>			
2	1 (2%)	2 (4%)	1
3	49 (98%)	48 (96%)	
Calcification	6 (12%)	4 (8%)	0.741
Post-dilatation balloon	8 (16%)	1 (2%)	0.031*
Pre-dilatation balloon	8 (16%)	1 (2%)	0.031*
<i>Pressure of Deployment</i> (atm):			
Mean ± SD	15.68±1.82	16.31±1.92	0.095
<i>Stent Diameter (mm):</i>			
Mean ± SD	3.02±0.4	3.41±0.29	<0.001*
<i>Stent Length (mm):</i>			
Mean ± SD	25.44±9.22	20.31±4.88	<0.001*
<i>Site:</i>			
LAD	26 (52%)	5 (10%)	0.002*
RCA	20 (40%)	27 (54%)	0.132
CX	8 (16%)	16 (32%)	0.787
Diagonal	2 (4%)	1 (2%)	0.557
OM	3 (6%)	1 (2%)	0.307
Ramus	1 (2%)	0 (0%)	1
SVG	1 (2%)	0 (0%)	1
<i>Number of stents:</i>			
1	28 (56%)	31 (62%)	0.241
2	17 (34%)	18 (36%)	
3	5 (10%)	1 (2%)	

- Data expressed as Mean ± SD or median (IQR: Inter-quartile range) for continuous variables and No. of patients categorical variables (%).

ISR : Instent restenosis.

TIMI: Thrombolysis in myocardial infarction.

CX : Circumflex artery.

LAD: Left anterior descending.

OM : Obtuse marginal.

RCA: Right coronary artery.

SVG: Saphenous vein graft.

Table (2): The previous Procedural and Quantitative Coronary Angiography (QCA) character differences between the ISR and no ISR.

Variables	ISR (n = 50)	No ISR (n = 50)	p-value
De-novo PCI	9 (18%)	28 (56%)	0.790
Type B2/C lesions	6 (66.66%)	11(39%)	0.080
<i>Area stenosis %:</i>			
Mean ± SD	79.11±18.2	74.32±17.9	0.188
<i>Diameter stenosis %:</i>			
Mean ± SD	73.18±20.6	71.63±19.7	0.701
<i>Max LA (mm²):</i>			
Median	4.93	5.12	0.617
IQR	0-11.94	0-10.71	
<i>Max LD (mm):</i>			
Median	2.365	2.381	0.336
IQR	0-3.9	0 – 4.1	
<i>MLA (mm2):</i>			
Mean ± SD	1.47±0.75	2.86 ±1.21	0.897
<i>MLD (mm):</i>			
Mean ± SD	0.98±0.44	1.91±0.69	<0.0001
<i>Lesion length (mm):</i>			
Median	35.9±19.7	38.4±20.8	0.429
IQR	4-48	5-41	
<i>Average reference area (mm²):</i>			
Mean ± SD	7.04±2.69	7.12±2.77	0.884
<i>Distal reference area (mm²):</i>			
Median	3.97	4.21	0.692
IQR	0-16.6	0-15.8	
<i>Proximal reference area (mm²):</i>			
Mean ± SD	9.82±3.11	9.71±3.07	0.859
<i>Average reference diameter (mm):</i>			
Mean ± SD	2.77±0.69	2.82±0.70	0.720
<i>Distal reference diameter (mm):</i>			
Mean ± SD	2.06±1.09	2.22±1.21	0.489
<i>Proximal reference diameter (mm):</i>			
Mean ± SD	3.48±0.62	3.32±0.59	0.189

- Data expressed as Mean ± SD or median (IQR: Inter-quartile range) for continuous variables and No. of patients categorical variables (%).

(%).

PCI : Percutaneous coronary intervention.

ISR : Instent restenosis.

Max LA: Maximum lumen area.

MLA: Minimum lumen area.

MLD: Minimal lumen diameter.

Table (3): Differences between focal ISR and diffuse-type regarding the previous PCI procedural data.

Variables	Focal (n = 27)	No Focal (n = 23)	p-value
Residual stenosis	0 (0%)	3 (13.0%)	0.09
Dissection	0 (0%)	2 (8.7%)	0.207
<i>TIMI:</i>			
2	0	1	0.283
3	27 (100%)	22 (95.6)	
Calcification	3 (11.1%)	3 (13.0%)	0.585
Post-dilatation balloon	1 (3.7%)	7 (30.4%)	0.010*
Pre-dilatation balloon	1 (3.7%)	7 (30.4%)	0.010*
<i>Deployment pressure (atm):</i>			
Mean ± SD	15.93±2.04	15.39±1.53	0.306
<i>Diameter (mm):</i>			
Mean ± SD	3.04±0.31	2.62±0.56	0.002*
<i>Length (mm):</i>			
Mean ± SD	22.11±7.91	29.35±9.26	0.005*
<i>Site:</i>			
LAD	8 (29.6%)	18 (78.3%)	<0.001*
RCA	7 (25.9%)	13 (56.5%)	0.028*
CX	4 (14.8%)	4 (17.4%)	1
Diagonal	2 (7.4%)	0 (0%)	0.183
OM	3 (11.1%)	0 (0%)	0.239
Ramus	1 (3.7%)	0 (0%)	1
SVG	1 (3.7%)	0 (0%)	1
<i>Number of stent:</i>			
≥2	10	12	0.284
1	17	11	

- Data are presented as mean ± SD or n (%).
 PCI: Percutaneous coronary intervention.
 ISR: Instent restenosis.
 TIMI: Thrombolysis in myocardial infarction.
 CX: Circumflex artery.
 LAD: Left anterior descending.
 OM: Obtuse marginal.
 RCA: Right coronary artery.
 SVG: Saphenous vein graft.

Discussion

Restenosis was documented in 50 patients (50%) with 59 lesions and target lesion revascularization was required in 38 patients. So the prevalence of ISR was 50%. Regarding the gender, The ISR is common in males than females with Statistical significance differences (p -value < 0.001). This opposed one study [6] which showed that females had more risk. Presence of DM is associated with ISR (p -value < 0.001).

Diabetes continues to be an independent risk predictor of restenosis, in conformity with that reported in published articles [7-9], but in contrast with other one [10].

Table (4): Qualitative Coronary Angiography (QCA) of the area and diameter measurements differences between focal and diffuse ISR.

Variables	Focal (n = 27)	No Focal (n = 23)	p-value
<i>Average reference diameter (mm):</i>			
Mean ± SD	2.97±0.46	2.54±0.83	*0.024
<i>Distal reference diameter (mm):</i>			
Mean ± SD	2.51±0.51	1.54±1.37	*0.001
<i>Proximal reference diameter (mm):</i>			
Mean ± SD	3.44±0.49	3.53±0.75	0.611
<i>Average reference area (mm²):</i>			
Mean ± SD	7.29±2.09	6.74±3.29	0.468
<i>Distal reference area (mm²):</i>			
Mean ± SD	5.12±1.98	3.27±4.01	0.039*
<i>Proximal reference area (mm²):</i>			
Mean ± SD	9.48±2.55	10.21±3.68	0.409

- Data expressed as Mean ± SD or median (IQR: Interquartile range) for continuous variables and No. (%) of patients for categorical variables.
 ISR: Instent restenosis.

Previous angiographic and procedural variables were analyzed in this study and showed that ISR is common in long segment with small diameter (p -value < 0.001), in conformity with that reported article [11]. Non-focal (diffuse-type) restenosis was documented in 23 (46%) patients of the fifty ISR patients. This study showed that pre-stenting minimal lumen diameter (MLD), pre and post balloon dilatation, DM, Male sex, LAD, RCA, and the stent length are independent predictors of diffuse-(non-focal) type ISR.

Summary and Conclusion:

The present study was conducted upon 100 patients (68 males, 32 females; mean age 44±24 years) to determine the prevalence, predictors, management and 6 months follow up complications

of PCI. In a retrospective-prospective descriptive design. Patients with clinical evidence of stable or unstable coronary artery disease with a history of previous PCI were included in the study according to the inclusion criteria. All the included population underwent the following diagnostic work-up: Clinical evaluation, Lab work, ECG, Echo, coronary angiography with Qualitative Coronary Angiography analysis, management according to his presentations then followed-up for 6 months. Restenosis was documented in 50 patients (50%) with 59 lesions and target lesion revascularization was required in 38 patients.

We demonstrated that male gender (p -value <0.001), DM (p -value <0.001), the longer and smaller stents (p -value <0.001 for both), the use of pre and post balloon for dilatations (p -value <0.031), mean pre stenting MLD (p -value <0.0001) and LAD Lesions (p -value <0.002) were predictors of ISR. As well as DM, Stent length and pre stenting minimal lumen diameter (MLD) which were independent predictors of ISR. Non-focal restenosis was documented in 23 (46%) patients of the fifty ISR patients. This study showed that pre-stenting minimal lumen diameter (MLD), pre and post balloon dilatation, DM, Male sex, LAD, RCA, and the stent length and diameter are predictors of diffuse (non-focal) type ISR.

Recommendations:

- 1- Pre and post balloon dilatation shouldn't be done routinely and direct stenting by using more short and large stents is advisable.
- 2- Further studies using IVUS or OCT are needed for better early detection and management of ISR.

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الطيف السريري وعلاج المرضى الذين يعانون من ضيق الدعامات فى الشريان التاجى

تعتبر ضيق وانسداد الدعامات من أكثر المشاكل التى يعانى منها مرضى قصور الشرايين التاجية الذين خضعوا للقسطرة العلاجية وتركيب دعامة دائرية وهذا البحث قدم لمعرفة الاسباب والعوامل ومضاعفات هذه الحالة.

ان أمراض القلب والأوعية الدموية باتت شائعة بكثرة والعلاج بالقسطرة العلاجية بات أهم وأفضل اساليب علاج مرضى القصور الحاد والجلطات القلبية بالشرايين التاجية وعلى الرغم من التقدم الملحوظ فى مجال الدعامة الدوائية الا أن ضيق وانسداد الدعامات اصبح منتشرأ بشكل ملحوظ بين هؤلاء المرضى ومن هنا لزم البحث وعمل الدراسات لمعرفة أسباب ومضاعفات تلك المشكلة حيث أن معدلات الوفاة سارت مرتفعة بنسبة كبيرة بسبب أمراض القلب والأوعية الدموية.

إن التشخيص المبكر لأسباب انسداد الدعامة يمكننا من بدء العلاج المناسب وتجنب مضاعفات هذا المرض.

هدفنا من هذه الدراسة هو تحديد عوامل الخطورة وأسباب ومضاعفات انسداد الدعامة الدوائية لمرضى قصور الشرايين التاجية.

أجريت هذه الدراسة على خمسين مريضاً من مرضى القصور الشريان التاجى بمستشفيات النهضة العام بالمملكة العربية السعودية.

خضع جميع المرضى المشاركين بالدراسة لفحص إكلينيكي شامل وتسجيل للتاريخ المرضى و تحليلات معملية بالدم مثل نسبة الكريتينين، السكر والدهون الثلاثية والكوليسترول وتم عمل رسم قلب كهربائى لجميع المرضى وتم عمل موجات فوق صوتية للقلب للمرضى وتم عمل قسطرة قلبية لجميع المرضى.

وضحت نتائج الدراسة أن معدل انتشار انسداد الدعامة الدوائية لمرضى قصور الشرايين التاجية حوالى ٢٪ ويكون أكثر فى الرجال عن النساء وخصوصاً فى مرضى السكرى.

أوضحت الدراسة عدم وجود ارتباط قوى بين التقدم فى العمر و وجود انسداد للدعامات، وعدم وجود ارتباط بين الانسداد للدعامات وعوامل الخطورة من ارتفاع ضغط الدم والتدخين وزيادة الدهون او التاريخ العائلى لقصور الشريان التاجى.

لم تظهر الدراسة وجود ارتباط بين وجود الانسداد للدعامات وحالة المريض فى المتلازمة القلبية الحادة أو كفاءة عضلة القلب بالإيكو.

أظهرت نتائج الدراسة أنتشار المضاعفات و حدوث الوفاة بين مرضى الانسداد لدعامات النوع المنتشر عن الموضعى ولكنة لم يكن ذو أهمية احصائية.

وضح التحليل الاحصائى للمتغير المنفرد وجود أهمية احصائية بين مرضى الانسداد النوع المنتشر مع طول الدعامات وصغر حجمها وكونها فى الشريان الايسر النازل او الايمن. كما وضح التحليل الاحصائى للمتغيرات المتعددة أهمية احصائية لصغر قطر الدعامات بعد وضعها واستخدام البالون قبل وبعد التركيب كعوامل خطورة منفردة للإصابة بالانسداد لدعامات النوع المنتشر.

ونستنتج من هذه الرسالة أن مرض الانسداد لدعامات الشريان التاجى النوع المنتشر موجود بصورة كبيرة فى مرضى قصور الشرايين التاجية ويعد صغر قطر الدعامات بعد وضعها واستخدام البالون قبل وبعد التركيب من مسببات الخطورة لهذا المرض.