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ADULT CARDIOLOGY

Frequency of In-Stent Restenosis among Different 2nd/3rd Drug Eluting Stents in Patients Presenting with ACS/Angina at Tertiary Cradiac Care Centre

Shakir Ghaffar, Waheed-ur-Rehman, Alam Khan, Muhammad Amad Abbasi, Sajjad Ali, Muhammad Naeem Tariq, Zeeshan Arif, Syed Khurram Shahzad, Javeria Kamran

Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: Primary objective was to determine the frequency of in-stent restenosis (ISR) among second/third generation drug eluting stents (DES), diagnosed angiographically in cardiac catheterization laboratory either in emergency settings or elective stage procedure and to determine the risk factors precipitating ISR.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Tertiary Cardiac Care Center of Rawalpindi Pakistan, from Nov 2021 to Apr 2022.

Methodology: After hospital ethical committee approval, medical data of consecutive patients were analyzed. Clinical and bio data were obtained followed by admission. Risk factors for atherosclerosis obtained along with baseline investigations and echocardiogram obtained to calculate ejection fraction. Classified interventional cardiologists analyzed angiographic images and confirmed the presence of ISR. Details of previous angioplasty and type of stent were documented.

Results: Out of total 137 patients, 98(72%) were males and 39(28%) females. 94(68%) patients were diabetic, 102(72%) were hypertensive, 72(52%) had dyslipidemia, 56(40%) were smokers, and 32(23.35%) strong family history of CHD. After coronary angiography we found that frequency of ISR was 32(23%) in patients who had Xlimus sirolimus stent, 34(24.8%) patients had Xience (everolimus eluting stent), 33(24%) had Ultimaster (sirolimus eluting stent), 38(27%) had Biomatrix stent with *p*-value =0.25.

Conclusion: The clinical presentation of ISR is usually with angina in all new generation DES. There was no statistically significant difference in terms of ISR among second/3rd generation DES. DES ISR not only depends upon the type of DES used but also depends upon multiple patient and procedure related risk factors.

Keywords: Bare metal stents, Drug eluting stents, Percutaneous coronary intervention.

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INTRODUCTION

Restenosis is the most common complication of coronary intervention.[1] After BMS era now use of drug eluting stents (DES) is best choice for stenosis treatment even in patients with high risk of bleeding.re stenosis rate was significantly reduced with newer DES technology.[1,2] Although restenosis still develops after modern DES in 5 to 10% patients,[3,4] and this has become a common clinical problem despite widespread use of 3rd generation DES.[5,6] however, if we compare it with BMS stent restenosis, DES restenosis treatment is associated with poor long-term outcomes; present data suggest that after repeat stenting, 10-20% of these patients go on to develop recurrent restenosis.[7,8]

Coronary intervention with stenting is best treatment modality for both acute coronary syndrome and stable ischemic heart disease. Most common complication after stenting is stent thrombosis and in-stent restenosis (ISR).[9]

In one previous study, the factors identified in patients with post percutaneous coronary intervention (PCI) ISR were: smoking (37.6%), hypertension (65.5%), Diabetes Mellitus (45.1%), hyperlipidemia (41.9%) and positive family history of coronary heart disease 16 (10.7%) Another study on patients presenting with ISR after angioplasty revealed that 66.7% were males, 46.7% were smokers, 66.7% had a history of hypertension, 43.3% had a history of diabetes mellitus and 43.3% were found to have hyperlipidemia.[10]

The present study was designed to determine the frequency of instent restenosis among three types of drug eluting stents in patients presenting with Acute Coronary Syndrome/Angina. The results of this study will provide us not only with local magnitude of the factors leading to ISR as mentioned above, but also will compare its ratio between different DES. The results of this study will be projected to local cardiologists and based upon results of this study; we may be able to

Correspondence: Waheed-ur-Rehman; Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan

draw recommendations for future which may include further research on similar context for establishing associations and for constant monitoring of at-risk population after PCI. This will help us in reducing the morbidity due to PCI and ISR in our local adult population.

The primary objective of this study was to determine the frequency of ISR among 2nd/3rd generation dug eluting stents, diagnosed angiographically in cardiac catheterization laboratory either in emergency settings or elective stage procedure. The secondary objective was to determine the most important risk factors as a comorbid precipitating ISR.

METHODOLOGY

In-stent restenosis (ISR) was defined by the presence of >50% diameter stenosis inside the stent or its proximal or distal edges (adjacent 5mm segments) by visual angiogram. Silent ischemia was defined as ischemia identified on myocardial perfusion scan in the absence of symptoms.

This analytical cross-sectional study included consecutive (n=137) patients with clinically culprit ISR, presented to Armed Forces Institute of Cardiology, Rawalpindi Pakistan from 1st November 2021 to 30th April 2022, six months, after approval of this study was obtained from our institution ethical review board (IERB letter # 24/12/R&D/2021/128).

Sample Size: With reference to the 10% prevalence[3,4] of instant restenosis the sample size was calculated to be n=138 at 95% CI and 5% margin of error.

Inclusion Criteria: All patients of both genders (male & females) having age 30 to 75 years with previous angioplasty and now presenting with Angina or sudden onset of ACS related symptoms (as per operational definitions) and patients with ISR on repeated angiography were included in the study.

Exclusion Criteria: Patients with renal failure and hepatic failure

After hospital ethical committee approval, medical data of these patients were analyzed. Clinical and bio data were obtained followed by admission. Risk factors for atherosclerosis obtained along with baseline investigations and echocardiogram obtained to calculate ejection fraction. Classified interventional cardiologists analyzed angiographic images and confirmed the presence of ISR. Details of previous angioplasty and type of stent were documented

After presentation to outpatient or ER, patient was admitted to ward. Clinical incidents over the period of hospitalization were divided into patients with ACS (acute coronary syndrome) presenting along myocardial infarction (MI) and unstable angina (UA) and non-ACS patients included silent ischemia /stable angina.

Diagnosis of MI was done on the basis of universal definition and was categorized into STEMI (ST-elevation myocardial infarction) and NSTEMI (non-ST elevation myocardial infarction). Typical chest pain that increases by physical exertion and is partially or completely reduced by rest and/or nitrates was labelled as stable angina. If chest pain develops at rest or occurs with least exertion with or without ST-T changes on ECG is defined as unstable angina. Cardiac biomarkers are negative. Unstable angina patient with biomarkers positive tests were labeled as having NSTEMI.

Continuous variables were described using mean and standard deviation. Frequencies and percentages (n, % respectively) were calculated for categorical variables. Chi-square test was used for Proportion of ISR among 2nd/3rd generation drug eluting stents among patients in acute settings and elective stage procedures by keeping confidence interval of 95 and 5% margin of error. *p*-value of ≤ 0.05 was taken as an indicator of statistical significance. Statistical analysis was carried out using SPSS software for windows (version-22).

RESULTS

In this study we reviewed (n=137) patients presented to us in emergency of a tertiary cardiac care center, and those admitted from outpatient department for elective stage procedure in six month duration, from November 2021 to April 2022.

Out of these (n=137) patients, 78(56.9%) presented with definite ACS, out of these (n=78) patients, 42 (30.6%) were unstable angina, 33(24%) NSTEMI, and only 3(2.1%) STEMI as shown in Table-I. (n=59) patients presented to OPD presented with stable angina had significant ISR on coronary angiography. Out of these patients 23(38.9%) patients had increased frequency of exaggerated chest pain symptoms, 18(30.5%) patients had poor drug compliance, and remaining 18(30.5%) patients were diabetic, smokers.

Table-I: ACS/Non-ACS presentation (n=137)

Variables		n(%)
ACS (n=78)	**STEMI**	3(2.15%)
	NSTEMI	33(24%)
	UA	42(30.6%)
Non ACS		59(43%)

While looking at patients' gender and comorbidities, out of (n=137) patients, 98(72%) were males and 39(28%) females. 94 patients were diabetic, 72(52.6%) had dyslipidemia (72%), 56(40%) were smokers, 32 strong family history of CHD, and 52(68%) patients were hypertensive (Table-II).

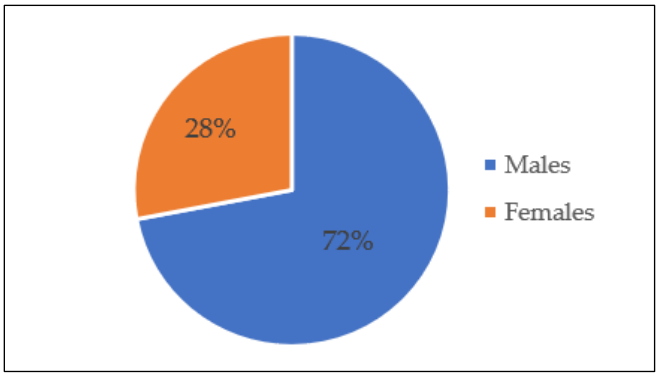

Figure-1: Gender distribution

Table-II: Clinical Characteristics of patients

Clinical Characteristics		n(%)
Diabetes Mellitus		94(68%)
Hypertension		102(72%)
Smoking		56(40%)
Dyslipidemia		72(52%)
Dual Antiplatelet Compliance		126(91%)
LV Functions	<30%	42(30%)
	30-45%	66(48%)
	>45%	29(21%)

On reviewing patients previous record, had found our (n=137) patient population had four different types of drug eluting stents, i-e, Xience (everolimus eluting stent), Ultimaster (sirolimus eluting stent), Biomatrix flex/Alpha (biolimus eluting stent) and Xlimus (sirolimus eluting stent).

After coronary angiography we found that frequency of ISR was 32(23%) in patients who had Xlimus sirolimus stent, 34(24.8%) patients had Xience (everolimus eluting stent), 33(24%) had Ultimaster (sirolimus eluting stent), 38(27%) had Biomatrix stent. All these patients underwent successful treatment and in stable condition shifted to coronary care unit and discharged on guideline directed medical therapy. Chi square test revealed a statistically non-significant association of type of drug eluting stents with the ISR presence (p>0.05; CI=95%; α=5%) (Table-III). Different lesion characteristics are depicted in Table-IV.

Table-III: Proportion of ISR among 2nd /3rd generation Drug Eluting Stents

Type of Drug Eluting Stents	ISR Presence	*p*-value
Xience	34(24.8%)	0.25
Xlimus	32(23.0%)	
Biomatrix	38(27.0%)	
Ultimaster	33(24.2%)	

Table-IV: Lesion characteristics

Lesion type	A	22(16%)
	B	44(32%)
	C	71(51%)
Lesion diameter	≤ 2.5mm	92(67%)
	>2.5	45(32%)
Lesion length	≤35mm	54(39%)
	>35mm	83(60%)
Number of stents	1	22(16%)
	2	54(39%)
	3	61(44%)
Artery involved	LAD	54(39%)
	LCX	44(32%)
	RCA	39(28%)
CTO		61(32%)

DISCUSSION

Our study was conducted just to determine the frequency of ISR in different drug eluting stents presented to our institute, irrespective of their clinical presentation and comorbidities.

One of the most important problems after stent deployment is stent thrombosis and in stent re stenosis. Stent thrombosis usually present with acute severe chest pain collaborated with myocardial infarction (MI) in the stented artery area, whereas ISR usually presents with stable or unstable angina. Stent thrombosis is usually caused by procedural complications like edge dissection, malapposed stent struts or poor compliance with dual antiplatelets and that usually has acute or subacute presentation.

If a patient presents with target lesion failure shortly, its unusually to be caused by neo intimal hyperplasia or neo atherosclerosis but actually caused by procedure related factors.

In BMS neo intimal hyperplasia was one of most important factors resulting in re stenosis and patient would usually present with ISR in 6 months to 1 year.

In bare metal stents frequency of in stent restenosis was in 10-30% of the interventions and was one of the most important clinical problem post stent deployments.[11,12] However, it's not only the stent design/polymer that contributes solely for restenosis,

there are certain other Risk factors for in-stent restenosis. These risk factors could be divided into factors like length of stent, diameter of vessel, ostial lesions, stent fracture, CTO,[13] or patient-related risk factors like diabetes mellitus, female gender, genetic polymorphism, hypertension and lipid profile.[14,15]

After modification in structure and design frequency of ISR has been significantly reduced among new generation stent. In one randomized controlled study EES stent was compared with SES. Base line characteristics are same among with groups. The in-segment binary restenosis rate was 7.3% in EES group VS 2.7% in SES group showing statistically significant difference (7.3% vs. 2.7%, p=0.046)

The new generation DES were designed and over the time modified to decrease re stenosis rate and improve deliverability of stent to site of lesion. These modifications involves different drugs (zatorolimus, biolimus) and enhancements in stent platform (i.e., thick-strut stainless steel vs thin-strut cobalt chromium), polymer (thinner and/or biodegradable), (luminal VS abluminal drug coating). Various randomized studies have confirmed that the next-generation Everolimus eluting stents is more useful to the first-generation paclitaxel-eluting stent (PES) in relations of thrombosis and repeated revascularization.[16,17]

Certain studies showed that if a patient presents with troponin-positive acute coronary syndrome, it might be predictor of adverse events in future after treatment of ISR.[18,19] However, In contrast, another observational study by Steinberg *et al*. showed that there is no difference in terms of subsequent adverse events.[20]

The effectiveness of a Drug eluting stent is highly dependent on its components: active pharmacologic drug, stent platform and drug carrier. Newer modifications in DES technology have more anti-inflammatory, immune modulatory, and/or anti proliferative agents to be released in appropriate amounts at the site of arterial injury during the initial 30-day healing period.[21,22]

LIMITATIONS OF STUDY

The exact mechanism that why DES restenosis in some patients and in some segments within the same patient are still unknown but probably Biological, technical and mechanical, factors has important contribution in ISR after DES implantation.

CONCLUSION

The clinical presentation of ISR is usually with angina in all new generation DES. There was statistically insignificant difference in terms of ISR among 2nd and 3rd generation DES. DES ISR not only depends upon the type of DES used but also depends upon multiple patient and procedure related risk factors.

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Conflict of Interest: None.

Author's contribution

Following authors have made substantial contributions to the manuscript as under:
SG: Principle investigator, Intellectual contribution, concept
WUR: Intellectual contribution, drafting the manuscript and critical review
AK: Data analysis, formatting and critical review
MAA: Critical review, manuscript writing and proof reading
SA: Data entry, drafting the manuscript and critical review
MNT: Manuscript writing, formatting and critical review
ZA: Proof reading, data collection and data analysis
SKA: Final approval, manuscript writing and proof reading
JK: Principle investigator, Intellectual contribution, concept
Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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