Original Article

Journal of Cardiovascular Medicine and Surgery
Volume 4 Number 3, July - September 2018
DOI: http://dx.doi.org/10.21088/jcms.2454.7123.4318.9

Study of Clinico-Etiological Profile of Patients with in-Stent Restenosis in Population of Western India

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Received on 06.08.2018
Accepted on 31.08.2018

Abstract

Background: Drug-eluting stents (DES) represent a significant improvement in the treatment of coronary artery disease as they decrease restenosis rates by approximately 50% compared with bare-metal stents. The study aimed to evaluate clinical, etiological factors and angiographic characteristics associated with occurrence of In-stent restenosis in of Bare metal (BMS) vs. Drug eluting stents. *Methods and Results:* The study included 200 patients of percutaneous coronary angioplasty during October 2014 to June 2016.Mean age of patients was 58.06±8.79 years with 140 (70%) were males and 60 (30%) were females. BMSand DES ISR (44.1% vs 56.3%) were diabetic (DM), (61% vs 84.4%) were hypertensive, (77.9% vs 56.3%) were dyslipidemic, (46.3% vs 21.9%) were smokers consecutively. Amongst the above risk factors, Diabetes (p-value 0.01) and smoking (p-value 0.028) were the two factors which had statistically significant correlation with severity of In-stent restenosis(ISR). Patients with BMS had more Non Focal ISR 98 (79.03%) than focal ISR 38 (50%) and the difference was statistically significant (p value <0.001). There was statistically significant difference (p =<0.05) between the stent diameter and the severity of ISR with less than 2.5 mm Diameter stents associated with more Non focal ISR. *Conclusion:* ES appears to reduce restenosis and clinical end points and to be more cost effective than BMS. Patientrelated factors (i.e. sex, Diabetes, smoking) are important variables that affect restenosis and, hence, the appropriate selection of devices and patients is crucial.

Keywords: Bare Metal Stent; Drug Eluting Stent; Restenosis; Risk Factor.

Introduction

Clinical in-stent restenosis (CISR) is defined as the presence of symptoms of myocardial ischemia and/or evidence of ischemia on functional tests after percutaneous coronary intervention (PCI). Drug eluting stents (DES) were specifically designed to decrease the high restenosis rates observed with bare metal stents (BMS) [1]. DES is associated with a distinct process linked with escalating and persistent inflammatory vessel wall reaction, fibrin deposition, and earlier and more frequent neo-atherosclerosis findings [2]. These surrogate findings may enhance the vulnerability of the first-generation DES ISR neointima, thereby increasing the ACS presentation propensity [3]. By contrast, second-generation DES conveys a safer preclinical performance with less prominent inflammatory reaction [4,5]. The incidence of ISR ranges from 3% to 20% of patients [6].

This study is conducted to evaluate clinical, etiological factors and angiographic characteristics associated with occurrence of In-stent restenosis.

Materials and Method

This prospective cross sectional study included 200 consecutive patients aged 18 years or older who were admitted with ISR who had undergone percutaneous coronary interventions with either BMS or DES from October 2014 to June 2016. Clinical, laboratory diagnostic, and operative reports, as well as the hospital and

postoperative course of each patient, were stored in a computerized database.

Exclusion of patients they had known hypersensitivity or contraindication to aspirin, paclitaxel, patient with platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, a WBC of <3,000 cells/mm^3, or Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions, Patients of stent thrombosis.

Method

Our study was approved by the Institutional Ethics Committee and the subjects gave informed consent. Percutaneous coronary intervention was done according to standard techniques through femoral or radial approach. All angiograms were analyzed by two independent observers using visual inspection. The angiographic pattern of In-stent restenosis should be defined according to the Mehran's classification [7].

Classification of ISR [7]

Class I: Focal ISR group. Lesions are <10 mm in length and are positioned at the unscaffolded segment (i.e., articulation or gap), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR)

Class II: "Diffuse intrastent" ISR. Lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).

Class III: "Diffuse proliferative" ISR. Lesions are 10 mm in length and extend beyond the margin(s) of the stent(s).

Class IV: ISR with "total occlusion." Lesions have a TIMI flow grade of 0.

Statistical analysis

All statistical analyses were performed with commercially available software (SPSS version 20.0, SPSS, Inc, Chicago, Illinois). Continuous variables are expressed as mean±SD and categorical data as percentages. Comparisons between BMS and drug eluting stents were performed with a 2-tailed Student's paired t test. Categorical variables were compared using chi-square statistics. The independent variables, which by bivariate analysis had p value <0.05 were included in multivariate analysis. To identify factors of independent variables associated with ISR, a multivariate analysis was performed using binary logistic regression test. To identify independent variables that had some effect on dependent variables, the effect was evaluated and expressed as Odds Ratio (OR). A p value of <0.05 was considered significant.

Results

The demographic and clinical presentation of the population is presented in Table 1. Amongst 200 patients with ISR, 136 patients had BMS implanted and 64 patients had DES implanted.136 patients of BMS ISR, most common pattern of ISR was diffuse 80 (58.82%) (OR 1.49 95% CI 0.95 to 2.34, p=0.08) followed by focal 38 (27.94%) (OR 5.48 95% CI 3.39 to 8.84, p=<0.0001), proliferative in 12 (8.82%) and obstructive 6(4.41%). Amongst the 10 patients with 1st Gen DES ISR, most common pattern of ISR was diffuse 4 (40%) and proliferative 4 (40%), and focal 2 (20%). Amongst the 54 patients with 2nd Gen DES ISR, most common pattern of ISR was focal 36 (66.66%) followed by diffuse 14 (25.92%) and proliferative in 4 (7.40%) patients.

Clinical presentation of the patients was 32% presented with chronic stable angina, 49.5%, unstable angina, 17.5% presented with NSTEMI whereas 1% presented with STEMI. 136 patients with BMS 35.3% presented with CSA (OR 6.38 95% CI 3.36 to 12.08, p= <0.0001), 47.8% presented with UA (OR 2.17 95% CI 1.44 to 3.25, p=0.0002), 15.4% presented with NSTEMI (OR 10.02 95% CI 6.26 to 6.04, p=<0.0001), 1.5% presented with STEMI. 64 Patients with DES implant, 25% presented with CSA (OR 0.84 95% CI 0.54 to 1.37, P=053), 53.1% patients presented with UA (OR 0.48 95% CI 0.32 to 0.72, P= 0.0004), 21.9% patients presented with NSTEMI (OR 2.22 95% CI 1.39 to 3.55, p= 0.0009).

Stent diameters less than 2.5mm were strongly associated with BMS then DES ISR (p value 0.034). 136 patients of BMS ISR, there were 53 (38.97%) patients with stent size less than 2.5mm. In 64 patients with DES ISR maximum number of patients 24 (37.5%) had stent length less than 2.5mm.There was statistically significant difference between stent length and ISR with stent length more than 3.5mm strongly associated with ISR (p value 0.005).

Based on bivariate analysis, we found nine independent variables with p <0.05 including age, smoking, DM, hypertension, type of stent, length of stent and vascular diameter. The independent variables with results of bivariate analysis of p <0.05 were included in the multivariate analysis

Table 1: Demographic and clinical presentation of the population

Sr.no	Variable		N (%)
1	Sex	Male	140(70.0)
		Female	60(30.0)
2	Clinical presentation	EA	64(32.0)
		UA	99(49.5)
		NSTEMI	35(17.5)
		STEMI	2(1.0)
3	Diabetes Mellitus-II		90(45.0)
4	Hypertension		119(59.5)
5	Dyslipidemia		160(80.0)
5	Smoking		99(49.5)
6	Vessel	LAD	95(47.5)
		LCX	35(17.5)
		RCA	52(26.0)
		BMS	136(68.0)
7	Stent type	DES	64(32.0)
		BMS	10(5)
8	Stent diameter	2.5	30(15.0)
		2.75	3(1.5)
		2.75	67(33.5)
		3	78(39.0)
		3.5	16(8.0)
		4	4(2.0)
9	Stent length	20-25	76(38.0)
		30-35	1(0.5)
		35-40	65(32.5)
		>40	12(6.0)
10	Type of ISR	Focal	76(38.0)
		Diffuse	98(49.0)
		Proliferative	20(10.0)
		Obstructive	6(3.0)

*EA, effort angina; †UA, unstable angina; ‡NSTEMI, non ST-elevation myocardial infarction; §STEMI, ST elevation myocardial infarction;|| LAD, left anterior descending; #LCX, left circumflex; **RCA, right coronary artery; *BMS, bare metal stent; †DES, drug eluting stent

Table 2: Bivariate Analysis

		Correlations							
		DM	**HTN**	**Dyslipidemia**	**Smoking**	**BMS=1, DES=2**	**Stent diameter**	**Stent length**	**1=focal, 2= non focal**
Diabetes Mellitus-II	Pearson Correlation	1	.454**	.050	.170*	.026	.264**	-.032	.170*
Hypertension	Pearson Correlation		1	-.050	.138	-.054	.134	.236**	.031
Dyslipidemia	Pearson Correlation			1	.045	.075	.059	-.091	-.185**
Smoking	Pearson Correlation				1	.093	.079	-.037	.157*
BMS=1,DES=2	Pearson Correlation					1	.095	.121	-.302**
Stent diameter	Pearson Correlation						1	.048	-.098
Stent length	Pearson Correlation							1	-.082

**Correlation is significant at the 0.01 level (2-tailed);*Correlation is significant at the 0.05 level (2-tailed)

*DM, diabetes mellitus-II; †HTN, hypertension; ‡BMS, bare metal stent; §DES, drug eluting stent

(Table 2: Bivariate). The results of multivariate analysis using binary logistic regression test demonstrated that there were independent variables that had significant correlation with ISR (Table 3: Multivariate). 90 (45%) patients with DM and 110 (55%) without DM. Among 90 patients, there were 60 (66.7%) patients with BMS ISR and 30 (33.3%) patients with DES ISR. In our study there was no statistical difference between DM and Non –Diabetic patients with respect to ISR (p value 0.83). Morphological pattern of ISR among different stents is presented in Table 4. Amongst 136 patients with BMS ISR, most common pattern of ISR was diffuse in 80 (58.8%) patients while focal pattern 38 (59.4%) of ISR was most common amongst DES ISR. There was statistically significant difference between pattern of ISR and the type of stents used.

Diabetes mellitus & morphological pattern of ISR

In our study of 200 Patients, most common pattern of ISR among Diabetics was Diffuse 50 (55.6%) followed by focal ISR 26 (28.9%), proliferative ISR 12 (13.3%) and Obstructive ISR in 2 (2.2%). Among Non-diabetics patients focal ISR was found in 50 (45.5%) patients, Diffuse ISR in 48 (43.6%) patients, proliferative ISR in 8 (7.3%) patients and obstructive ISR in 4 (3.6%) patients. There was a trend of Diffuse pattern 50 (55.6%) of ISR being more common among Diabetics than Non-diabetics which was not statistically significant. focal pattern of ISR 50 (45.5%) was more common among Non-diabetics than diabetics and was statistically significant (p value 0.02).

Correlation between clinical features with severity of ISR

Amongst the baseline characteristics, prevalence of non-focal ISR 90 (72.58%) was more than Focal ISR 50 (65.78%) amongst males but it was not statistically significant (p value-0.1). Prior ACS during index procedure had more non focal ISR 84 (62.68%) than Focal ISR 50 (37.3%) but it was not statistically significant. Stable angina patients had more non focal ISR 40 (60.60%) than focal ISR 26 (39.39%) but it was not statistically significant (p value 0.77). Diabetes mellitus, hypertension, Dyslipidemia and Smoking were the most common risk factors found in our study. Amongst the above risk factors, Diabetes (p-value 0.01) and smoking (p-value 0.028) were the two factors which had statistically significant correlation with severity of ISR.

Patients with BMS had more Non Focal ISR 98 (79.03%) than focal ISR 38(50%) and the difference was statistically significant (p value <0.001). There was statistically significant difference (p value <0.05) between the stent diameter and the severity of ISR with less than 2.5 mm Diameter stents associated with more Non focal ISR. (Table 5).

Table 3: Multivariate analysis on factors associated with in-stent restenosis

	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Diabetes Mellitus-II	.003	3.468	1.516	7.934
Hypertension	.162	.567	.256	1.256
Dyslipidemia	.008	.287	.114	.722
Smoking	.044	2.396	1.024	5.604
BMS1DES2	.000	.183	.086	.389
Stent Diameter	.055	.353	.122	1.020
Stent length	.854	.996	.957	1.037

*C.I, confidence interval; †BMS, bare metal stent;‡ DES, drug eluting stent

Table 4: Morphological pattern of ISR among different stents

Type of ISR	BMS N=136	DES N=64	P-value
Focal	38(27.9%)	38(59.4%)	0.0001**
Diffuse	80(58.8)	18(28.1)	0.0001**
Proliferative	12(8.8%)	8(12.5%)	0.5783
Obstructive	6(4.4%)	0(0)	NA

**Correlation is significant at the 0.01 level (2-tailed)

Table 5: Angiographic and stent factors and severity of ISR

Variables		Focal ISR N=76	Non-focal ISR N=124	P-value
Vessels Treated				
Left Anterior Descending		33(43.42)	62(50)	0.36
Left Circumflex Artery		13(17.10)	22(17.74)	0.12
Right Coronary Artery		22(28.94)	30(24.19)	0.45
Type of stent	DES	38(50)	26(50)	<0.001**
	BMS	38(50)	98(79.03)	
Stent Length	<25mm	25(32.89)	52(41.93)	0.2
	26-30mm	27(35.52)	38(30.64)	0.47
	31-35mm	4(5.26)	8(6.45)	0.73
	36-40mm	20(26.31)	26(20.96)	0.38
Stent Diameter	<2.5	8(10.2)	28(22.58)	0.05*
	2.5-2.75	34(44.73)	40(32.25)	0.07
	2.75-3	22(28.94)	50(40.32)	0.1
	3-3.5	8(10.52)	6(4.83)	0.18

**Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed)

†BMS, bare metal stent; ‡ DES, drug eluting stent

Discussion

Restenosis rates vary and depend on many modifiable risk factors and angiographic characteristics of the patient population. Patient-related variables, such as age and sex, have not been consistently shown to predict restenosis [8]. In present study Mean age of patients was 58.06±8.79 years with maximum number of patients 80% in 50-60 age groups and more numbers of male. **S** Mohan et alreported mean age in patients who presented with restenosis of 52 years with majority of patients 45.5% between 46 to 60 age group [8].

In present study of 200 patients of ISR, Dyslipidemia, Hypertension, DM, Smoking were the most frequent risk factors. Dyslipidemia was the most common risk factor found in 80% patients, Hypertension in 59.5%, smoking in 49.5% and DM in 45%. Among BMS ISR, 44.1% were DM, 61% were hypertensive, 77.9% were Dyslipidemic and 46.3% were smokers. Among DES ISR, 56.3% were DM, 84.4% were hypertensive, 56.3.9% were Dyslipidemic and 21.9% were smokers. Various studies have related dyslipidemia with restenosis [9-11] they were conducted in a relatively small number of patients. Large prospective studies have not confirmed any such associations [12].

Out of these 68% patients had BMS ISR and 32% patients had DES ISR. There were 90 patients with Diabetes mellitus who had ISR, of which 44.1% patients had BMS and 46.9% patients had DES ISR. M. Kitoga et al shows ISR in 11% in a group of diabetes mellitus who received 58% BMS and 42% DES [13]. The association of diabetes with restenosis was initially observed in the National Heart Lung and Blood Institute percutaneous trans luminal coronary angioplasty registry [14]. Subsequent reports confirmed the risk of restenosis in diabetic patients to be 1.3 times the risk in non-diabetic patients using multivariable regression analysis. Insulin-dependent diabetes mellitus had a stronger relationship with restenosis [15].

Dyslipidemia, Hypertension, DM, Smoking were the most frequent risk factors of ISR [16]. Dyslipidemia was the most common risk factor found in 80% patients, Hypertension in 59.5%, smoking in 49.5% and DM in 45%. Among BMS ISR, 44.1% were DM, 61% were hypertensive, 77.9% were Dyslipidemic and 46.3% were smokers. Among DES ISR, 56.3% were DM, 84.4% were hypertensive, 56.3.9% were dyslipidemic and 21.9% were smokers.

The other study is Mohan et al. reported 51.7% as hypertensive, 6.9% were diabetic, 31% had dyslipidemia, 34.5% were smokers [8]. Comorbidities mentioned in above study were not comparable to the present study. Restenosis was found to be 1.2 to 1.7 times higher in acute coronary syndrome patients than in those with chronic stable symptoms (Mohan et al.). When we analyzed the occurrence of previous myocardial infarction we observed that it had occurred in 67% of the patients.

Marino BC et al. reported 28.2% patients with CSA, 45.5% and UA, 12.8% had NSTEMI and 4.5%

had STEMI [17]. The results of the above mentioned studies were comparable to the present study.

In present study BMS, most common vessel stented was LAD 43.4% patients followed by RCA 26.5%, LCX 18.4% patients and less than 10% patients had double vessel stenting. In DES implanted, most common vessel stented was LAD 56.3% patients followed by RCA 25%, LCX 15.6% patients and less than 10% patients had double vessel stenting. It was found that there was no statistical difference between vessel stented and type of stent used.

Mohan et al reported results comparable to our present study with no significant relationship between vessel stented and ISR [8].

Most common pattern of ISR was diffuse in 49% followed by focal 38%, proliferative 10% and obstructive 3%. BMS ISR, most common pattern of ISR was diffuse 58.82% followed by focal 27.94%, proliferative in 8.82% and obstructive 4.41%. DES ISR, most common pattern of ISR was focal 38%, diffuse 18% and proliferative 8%.

S Mohan et alin their study reported focal 50% as the most common pattern of ISR followed by diffuse in 21.90%, proliferative in 21.90% and obstructive in 6.30% patients [8]. Rathore s et alreported focal ISR (47%) more common in DES while Diffuse ISR was more common in BMS in their study [18]. The above results are comparable to our present study.

Most common stent diameters with BMS ISR, the range of 2.75mm–3mm including 53 (38.97%) patients and among 64 patients with DES ISR there were 32 (50%) patients with stent diameter 2.75mm -3mm. Stent diameters less than 2.5mm were strongly associated with BMS then DES ISR (p value 0.034).

In our study mean length of stents was 26.73 (±8.64) mm. BMS ISR; there were 38.97% patients with stent size less than 25mm. In DES ISR 37.5% patients had stent length less than 25mm. There was statistically significant difference between stent length and ISR with stent length more than 35mm strongly associated with ISR (p value 0.05).

S Mohan et al. reported mean length of stents 20.9 (±8.24) mm in their study group and no statistically significant relationship between stent length with respect to ISR in their study population [8].

Correlation between risk factors and severity of ISR

Diabetes mellitus, hypertension, Dyslipidemia and Smoking were the most common risk factors found in our study. Amongst the above risk factors, Diabetes (p-value 0.01) and smoking (p-value 0.028) were the two factors which had statistically significant correlation with severity of ISR. Prevalence of Non–focal ISR was more amongst hypertensive and dyslipidemic patients compared to focal ISR but it was not statistically significant. Kitahara et al reported in their study diabetes, hypertension and smoking had statistically significant correlation with severity of ISR with Non focal more common than focal ISR [19]. The above results are comparable to our present study.

Conclusion

DES appears to reduce restenosis and clinical end points and appear to be more cost effective than BMS. Stent type, stent length, stent diameter, smoking and diabetes mellitus are factors associated with ISR hence, the appropriate selection of devices and patient is crucial. Possibly, a less expensive DES will end the search for a stent that is cost effective and less prone to restenosis.

Funding sources: This work was supported by U.N. Mehta Institute of Cardiology and Research Centre itself and received no specific grant from any funding agency, commercial or not for profit sectors.

Disclosures: The authors have no conflict of interest to declare.

Key message: Drug Eluting Stent (DES), which maintain the mechanical advantages of BMS while delivering an anti-restenotic pharmacological therapy locally to the arterial wall, have been shown to effectively and safely reduce the amount of in-stent tissue that accumulates after stent implantation, resulting in significantly reduced rates of clinical and angiographic restenosis.

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