OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Cardiology**

Prolonged Outcomes Following the Treatment of Restenosis in Drug-Eluting Stents

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DOI: https://doi.org/10.36348/sjmps.2025.v11i03.003 | **Received:** 04.02.2025 | **Accepted:** 12.03.2025 | **Published:** 17.03.2025

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Abstract

Background: Drug-eluting stents have significantly lowered the risk of restenosis. However, how to treat restenosis inside a DES is unknown. While the number of severe adverse cardiovascular events (MACE) linked to drug-eluting stents (DES) has significantly decreased, stent thrombosis (STH) and in-stent restenosis (ISR) continue to be significant clinical problems. ***Materials and Methods:*** This observation cohort study was conducted in the Department of Cardiology, Universal Medical College and Northeast Medical College, Sylhet. During study period 2016 to 2020 Universal Medical College and 2020 to 2022 Northeast Medical College. Among 509 lesions treated with DES, 26 required clinically driven revascularization for ISR. We identified 26 consecutive patients who developed ISR, among them Homo-Stents (n=17), Hetero-Stents (n=5) and (n=4) treated by other. ***Results:*** Three cases (75%) in the other ISR group and one (20%) in the hetero-stent group had a history of congestive heart failure. Of the three groups, only one had clinical characteristics that were statistically significant ($p<0.05$), whereas the other two did not ($p>0.05$). In the hospital, the differences between the three groups at six and twelve months were not statistically significant ($p>0.05$). ***Conclusion:*** There is a high long-term rate of MACE associated with current DES therapies for ISR or STH.

Keywords: Drug-eluting stents, in-stent restenosis, major adverse cardiovascular events, myocardial infarction, percutaneous, coronary intervention.

INTRODUCTION

In-stent restenosis (ISR) is still the leading cause of target lesion failure after percutaneous coronary intervention (PCI), accounting for roughly 20% of target lesion revascularizations during a 10-year period.[1] Treatment of ISR is difficult due to its inherent proclivity for recurrence and varied responsiveness to existing methods, which are influenced by a complex interplay of clinical and lesion-specific factors [1].

In-stent restenosis (ISR) is a primary determinant of long-term percutaneous coronary intervention (PCI) failure and is traditionally defined as an angiographic reduction of ≥50% of the luminal diameter within a previously implanted stent or 5 mm segments proximally or distally ("stent edges") of a previously implanted stent [2].

Drug-eluting stents (DESs), through the integration of a metallic stent platform with the release of an ant proliferative medication, have substantially reduced ISR at 1-year incidences ranging from 2 to 4% to approximately 10%, depending on the individual risk profile and coronary artery disease complexity [3].

Drug-eluting stents (DES) have significantly reduced instent restenosis (ISR) and the need for revascularization compared with bare metal stents (BMS) [4,5]. In-stent restenosis (ISR) remains a challenging issue of percutaneous coronary intervention (PCI) even in the drug-eluting stent era [6]. Several techniques, including balloon angioplasty, plaque debulking, vascular brachytherapy, additional stent implantation, and use of a drug-coated balloon have been performed for the treatment of ISR. First-generation drug-eluting stents (DES), which inhibit intimal hyperplasia, have dramatically reduced the rate of in-stent restenosis (ISR) and subsequent target lesion revascularization (TLR) within the first year of stent

implantation compared with baremetal stents (BMS) [7].

The clinical outcomes after a DES failure and the correlates for recurrent DES ISR. We therefore aimed to report the clinical outcomes after DES failure treated with the available percutaneous strategies and to identify the covariates associated with recurrence of DES ISR.

METHODS

This observation cohort study was conducted in the Department of Cardiology, Universal Medical College and Northeast Medical College, Sylhet. During study period 2016 to 2020 Universal Medical College and 2020 to 2022 Northeast Medical College. Among 509 lesions treated with DES, 26 required clinically driven revascularization for ISR. We identified 26 consecutive patients who developed ISR, among them Homo-Stents (n=17), Hetero-Stents (n=5) and (n=4) treated by other. All patients had received aspirin, 325 mg, before the initial procedure, followed by ≥75 mg daily indefinitely, along with clopidogrel or ticlopidine for ≥6 months. The "homo-stent sandwich" technique consisted of restenting with the same DES, "hetero-stent sandwich" with a different DES, and "other" techniques included balloon angioplasty, insertion of a BMS, or brachytherapy. In-stent restenosis was defined as a >50% diameter stenosis within the first DES, or within 5 mm of its edges. The morphology of restenotic lesions has been described elsewhere. Major adverse cardiac events included death from all causes, myocardial infarction (MI), or target lesion revascularization (TLR). Myocardial infarction was defined as chest pain accompanied by new electrocardiographic changes consistent with ischemia and a creatine kinase (CK)-MB concentration >3-fold the upper normal limit. Target lesion revascularization was defined as re-intervention on the stented segment for chest pain or >70% stenosis on follow-up angiogram. Stent thrombosis was defined as an intraluminal filling defect with contrast staining on 3 sides, representing total or partial stent occlusion, present at the time of a clinically driven, repeat angiography. Patients were followed clinically at 6 months, and 1 and 2 years. Discrete variables are reported as percentages and continuous variables as means ±SD. Chi-square or Fisher exact tests were used to compare discrete variables and Student t tests for continuous variables. Actuarial 6- and 12-month rates of MACE were examined by the Kaplan- Meier method. Values of $p< 0.05$ were considered statistically significant.

RESULTS

Table 1: Clinical characteristics of the study patients (n=509)

	ISR (n=26)		No ISR (n=483)		P value
	n	%	n	%	
Age (≥60 years)	15	57.69	268	55.49	0.705
Male	18	69.23	302	62.53	0.376
Diabetes	11	42.31	150	31.06	0.063
Hypertension	20	76.92	294	60.87	0.046
Smoker	14	53.85	268	55.49	0.846
Hypercholesterolemia	24	92.31	380	78.67	0.011
Renal insufficiency	1	3.85	14	2.90	0.705
History of congestive heart failure	3	11.54	43	8.90	0.399
Cerebrovascular disease	4	15.38	60	12.42	0.662
Peripheral vascular disease	4	15.38	61	12.63	0.684
Prior myocardial infarction	15	57.69	133	27.54	0.001
Prior coronary artery bypass	10	38.46	136	28.16	0.053
Prior percutaneous coronary intervention	26	100.00	147	30.43	0.001
ST–segment elevation myocardial infarction at presentation	2	7.69	40	8.28	0.986
Non–ST-segment elevation myocardial infarction at presentation	1	3.85	72	14.91	0.037
Unstable angina at presentation	12	46.15	150	31.06	0.030
Stable angina at presentation	9	34.62	165	34.16	0.987
Silent ischemia at presentation	2	7.69	55	11.39	0.496
Multi-vessel coronary disease	15	57.69	318	65.84	0.286
Left ventricular ejection fraction <40%	4	15.38	58	12.01	0.597

P value reached from chi square test

Patients who developed ISR were more likely to be persons with higher prevalence of hypertensive, hypercholesterolemic, histories of MI, prior percutaneous coronary intervention, and unstable angina at presentation but lower prevalence of non–ST segment elevation myocardial infarction.

Table 2: Clinical characteristics of the ISR group (n=26)

	Homo-Stents (n=17)		Hetero-Stents (n=5)		Others (n=4)		p value
	n	%	n	%	n	%	
Age (≥60 years)	10	58.82	3	60.00	2	50.0	0.832
Male	12	70.59	3	60.00	3	75.0	0.889
Diabetes	6	35.29	3	60.00	2	50.0	0.489
Hypertension	12	70.59	4	80.00	3	75.0	0.976
Hypercholesterolemia	16	94.12	4	80.00	4	100.0	0.638
Smoker	8	47.06	3	60.00	3	75.0	0.225
Renal insufficiency	0	0.00	0	0.00	1	25.0	0.077
History of congestive heart failure	0	0.00	1	20.00	3	75.0	0.001
Cerebrovascular disease	2	11.76	1	20.00	1	25.0	0.771
Peripheral vascular disease	2	11.76	1	20.00	1	25.0	0.652
Prior myocardial infarction	9	52.94	3	60.00	2	50.0	0.760
Prior coronary artery bypass	6	35.29	2	40.00	2	50.0	0.887
Prior percutaneous coronary intervention	17	100.00	5	100.00	4	100.0	-
ST–segment elevation myocardial infarction at presentation	1	5.88	1	20.00	1	25.0	0.812
Stable angina at presentation	7	41.18	1	20.00	1	25.0	0.561
Unstable angina at presentation	8	47.06	2	40.00	2	50.0	0.855
Multi-vessel coronary disease	9	52.94	4	80.00	2	50.0	0.378
Silent ischemia at presentation	2	11.76	0	0.00	1	25.0	0.584
Left ventricular ejection fraction <40%	2	11.76	1	20.00	1	25.0	0.771

P value reached from chi square test

History of congestive heart failure was found 2 (20%) cases in hetero-stents and 3(75%) in others ISR group. Which was statistically significant ($p<0.05$) others clinical characteristics were not statistically significant ($p>0.05$) among three groups.

Table 3: ISR group in different follow up (n=26)

	Homo-Stents (n=17)		Hetero-Stents (n=05)		Others (n=04)		P value
	n	%	n	%	n	%	
In hospital							
Death	0	0.00	1	3.33	1	25	0.147
Myocardial infarction	1	5.88	0	0.00	0	0	0.755
All MACE	1	5.88	1	3.33	1	25	0.501
At 6 month	0	0.00	0		0	0	
Death	0	0.00	1	3.33	1	25	0.147
Myocardial infarction	0	0.00	0	0.00	0	0	-
All MACE	2	11.76	1	5.00	1	25	0.423
At 12 month	0	0.00	0		0	0	
Death	1	5.88	1	3.33	1	25	0.501
Myocardial infarction	0	0.00	0	0.00	1	25	0.103
All MACE	4	23.53	2	8.33	3	75	0.300

P value reached from chi square test

In hospital, at 6 month and at 12 month were not statistically significant ($p>0.05$) among three groups.

DISCUSSION

Patients who acquired ISR were more likely to be hypertensive and hypercholesterolemic, with history of MI, prior percutaneous coronary intervention, and unstable angina at presentation, but had a lower prevalence of non-ST segment elevation myocardial infarction. Mishkel *et al.*, [8] reported patients who developed ISR/STH were more likely to be persons with diabetes, hypertensive and hypercholesterolemic, more often had histories of MI, prior coronary artery bypass graft surgery, or percutaneous coronary intervention (PCI), and had a lower prevalence of non–ST segment elevation myocardial infarction (STEMI) and higher prevalence of unstable angina at presentation. Latib *et al.*, [9] DES-ISR resulted in an acute coronary syndrome in 13% of patients, and this acute presentation was more frequent with diffuse rather than focal or occlusive restenosis (21.1% vs. 9.2% vs. 14.9%; p= 0.012). In patients with occlusive

restenosis, the index lesion treated with a DES was more likely to be a chronic total occlusion (p= 0.0001) and possibly as a result longer stent lengths were implanted (p= 0.006). In a previous study from our center 8 of 250 DES-ISR lesions, we demonstrated that non focal DES-ISR is predictive of TLR at medium-term follow-up. A number of studies have examined the outcomes after the treatment of DES-ISR but many have been limited by the lack of adequate angiographic follow-up, [10-13] small sample sizes, [14-16] or short follow-up periods [11,12] Clinical long-term outcomes of 481 de novo DES-ISR lesions after their first percutaneous treatment, analyzed based on the pattern of restenosis. Similar to bare-metal stent restenosis, [17] DESISR is not a benign entity as it presents as an acute coronary syndrome in 13% of patients overall and in up to 20% of patients with diffuse restenosis.

In this study observed that there were two (20.0%) incidences of congestive heart failure in the hetero-stent group and eight (75.0%) in the rest of the ISR groups. While some clinical characteristics were statistically significant ($p<0.05$), others were not ($p>0.05$) across the three groups. Latib *et al.,* [9] reported DES-ISR was treated more often with repeat DES implantation rather than balloon angioplasty in all types of restenosis ($p<0.05$ for all comparisons). In diffuse and occlusive restenosis, the operator was more likely to implant a DES that eluted a different drug to the one that restenosed. Intravascular ultrasound usage was similar in the 3 groups. The duration of clinical follow-up was not statistically different between the 3 groups (p= 0.41). There were no in-hospital deaths or periprocedural revascularizations and the rate of periprocedural MI was similar in the 3 groups. Mishkel *et al.,* [8] reported that the clinical and angiographic characteristics, and the indications for repeat PCI among the 92 patients, and among the 3 treatment subgroups. Except for a higher prevalence of prior congestive heart failure in the "Others," these subgroups were similar. Three patients required 2 procedures during separate admissions for DES-ISR in separate lesions. Clopidogrel was administered for an average of 14.6±6.1 months.

In hospital, at 6 month and at 12 month were not statistically significant ($p>0.05$) among three groups. Mishkel *et al.,* [8] reported over a mean follow-up of 15.0±6.0 months, the overall rates of death, MI, and TLR were 8.7%, 2.2%, and 30.6%, respectively. The cumulative rates of in-hospital, 6-month, and 12-month adverse clinical events are summarized. Recurrent restenosis recurred in 28 patients (30.4%) and 33 lesions (30.6%). Of 6 patients who died after hospital discharge, 3 died of MI at 19, 105, and 212 days, respectively, 1 died of end-stage heart failure at 718 days, 1 died of respiratory failure at 511 days, and 1 died of unknown cause at 219 days of follow-up. Outcomes among treatment subgroups were statistically similar, although the "hetero-stent" treatment group tended to have lower MACE rates and need for repeat revascularization at 12 months. This might be explained by differences in the tissular response to the different DES, such that an initially poor response to 1 drug would be a signal to implant a DES that delivers another drug with different mechanisms of action. Finally, given the relatively high MACE rate in the DES ISR population, coronary artery bypass surgery should be considered as a viable treatment alternative for complex DES restenosis. Latib *et al.,* [9] reported about one-third of patients with DES-ISR experienced a MACE during long-term follow-up, irrespective of the pattern of restenosis treated at initial presentation. There were no significant differences between the groups in the rates of death or MI.

CONCLUSION

The difference was not statistically significant, although the hetero-stent therapy group had better 12-month outcomes than the other groups. This could be explained by variances in the tissular reaction to the various DES, such that an initial poor response to one medication would be a signal to implant another DES with a different mode of action. Finally, considering the relatively high MACE rate among DES ISR patients, coronary artery bypass surgery should be regarded as a possible therapy option for complex DES restenosis.

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