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Incidence and Management of In-Stent Restenosis in Patients with Drug-Eluting Stents

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ABSTRACT

Introduction: The most prevalent complication of cardiac intervention is restenosis. After the BMS period, drug-eluting stents (DES) are the most suitable choice for stenosis treatment, particularly for patients with a high risk of bleeding. The rate of restenosis was much lower with current DES technology. The introduction of drug-eluting balloons (DEBs) is a potential breakthrough for coronary revascularisation treatments, particularly in-stent restenosis. **Objective:** This retrospective study was carried out to find the incidence and management of in-stent restenosis in patients with drug-eluting strains. **Methods:** After the hospital ethics committee's permission, patients' medical data was evaluated. Clinical and personal data were acquired from medical records. Risk variables for atherosclerosis were collected, along with baseline labs and echocardiography, to assess the ejection fraction of each patient. Classified interventional cardiologists analysed angiographic pictures to confirm the existence of ISR. Details about prior angioplasty and the kind of stent were noted. All patients with considerable drug-eluting in-stent restenosis (DES-ISR) and eligible for therapy with DEB were included in the analysis. **Results:** Two hundred ninety-eight patients received at least one DES throughout the research period. ISR was identified in 50 individuals (16.77%). Thus, 50 patients who fulfilled the inclusion criteria were included in the study. 2% of the study population presented with STEMI, 22% with NSTEMI, 24% with UA, and 52% presented with non-ACS. Among all the patients that had ISR, diabetes and hypertension were the most common comorbidities found in the study population. Following coronary angiography, it was discovered that the frequency of ISR was 11(22%) in patients with Xlimus sirolimus stent, 10(20%) with Xience (everolimus-eluting stent), 13(26%) with Ultimate (sirolimus-eluting stent), and 16(32%) with Biomatrix stent. Twenty-eight patients with DES ISR who met the inclusion criteria received revascularisation with DEB. After a median of 18 months of follow-up, eight patients remained symptomatic, with 4 developing MACE, one resulting in cardiac death, and 3 requiring revascularisation. Thus, the overall MACE rate was 21%. There were two fatalities from non-cardiac causes. **Conclusions:** In all new-generation DES, ISR often manifests as angina. There was no statistically significant difference in terms of ISR between second- and third-generation DES.DEB technology, particularly for DES, holds potential for ISR. Our experience highlights the need for more data, including randomised studies in various patient groups.

INTRODUCTION

The most frequent side effect of coronary intervention is restenosis. (1). Even in individuals who have a high risk of bleeding, the use of drug-eluting stents (DES) is currently the best option for treating stenosis after the BMS era. (2). The rate of restenosis decreased considerably with the use of more recent DES technology. (3). Despite the widespread use of third-generation DES, restenosis still develops following modern DES in 5 to 10% of patients, and this has become a prevalent clinical

concern. (4). Compared to BMS stent restenosis, DES restenosis treatment is linked to unfavourable long-term results. Current studies indicate that 10–20% of these individuals' experience recurrent restenosis following repeat stenting. (5).

The drug-eluting balloon (DEB) was created to solve the problems that the bare metal stent (BMS) and drug-eluting stent (DES) have in common, that is, neointimal growth and thrombosis in the stent. (6). In theory, this system can uniformly administer the medication to the vessel wall, hence curbing the growth of the intima layer and decreasing the need for regular anti-platelet therapy to maintain vascular patency. (7).

This idea performed satisfactorily in preclinical research, with neointimal growth areas significantly reduced and balloon drug delivery that was adequate (90% in the first minute of inflating) (8). There aren't many clinical studies that follow them, but the ones that do show a positive decrease in late luminal loss, rates of restenosis, and major adverse cardiovascular events (MACE) in bifurcation lesions (9) . However, since their effectiveness in lesions with in-stent restenosis with DES (ISR DES) is most intriguing, more research is necessary to determine the proper role of the DEB in an interventionist's toolkit.

Thus, this research was carried out to find the Incidence and Management of In-Stent Restenosis with DES and the relative efficacy of management with DEB.

METHODS

This retrospective study was carried out at Fellow Interventional Cardiology NICVD Karachi, Pakistan in the duration from February, 2024 to July, 2024. After receiving clearance from the hospital's ethics committee, the medical data of these patients were analysed. Clinical and baseline data were collected. Risk variables for atherosclerosis were examined alongside baseline data and an echocardiography to determine the ejection fraction. Classified interventional cardiologists reviewed angiographic pictures and verified the existence of ISR. Details of prior angioplasty and kind of stent were documented.

In-stent restenosis (ISR) was characterised as the presence of a >50% diameter stenosis inside the stent or its proximal or distal margins (adjacent 5mm segments) on a visual angiography. Silent ischemia was characterised as ischemia found on a myocardial perfusion scan in the absence of symptoms. Clinical events during hospitalisation were divided into two groups. Individuals having ACS report myocardial infarction (MI), unstable angina (UA), and non-ACS patients with silent ischemia.

The research included all participants with ISR on repeat angiography. The analysis included all individuals with DES-ISR who were eligible for DEB treatment. Patients having a constriction in previous balloon-only treatment portions were excluded. Those patients who had renal or hepatic dysfunction were also excluded.

Patients were given 300 milligrams of aspirin and 300 milligrams of clopidogrel 6 hours before the surgery, and intravenous heparin was provided to maintain an activated clotting time of >250 seconds. The decision to provide glycoprotein IIb/IIIa inhibitors was up to the clinician. When preparing a lesion for DEB treatment, a compliant or non-compliant balloon inflated to its maximum luminal diameter based on its reference vessel size. To ensure optimal medication delivery to the vessel wall, DEB was utilised as the final step in lesion therapy, with no further ballooning required. The balloon-to-artery ratio for research participants was maintained at 0.9:1. At the ISR location; the DEB was inflated to its nominal pressure for 60 seconds. If a larger DEB was unavailable, two short-length DEBs were utilised successively to cover the lesion fully. At a residual stenosis of less than 20%, angioplasty was deemed successful. All patients were monitored after they were discharged. MACE comprised postprocedural cardiac mortality, myocardial infarctions (MIs), and the requirement for repeat revascularisation.

SPSS version 22 was used for data interpretation. The continuous parameters were characterised using mean and standard deviation. Categorical data were analysed using frequencies and percentages (n, %). The Chi-square test was used to measure the ISR proportion among 2nd/3rd generation drug-eluting stents. A p-value < 0.05 was considered statistically significant.

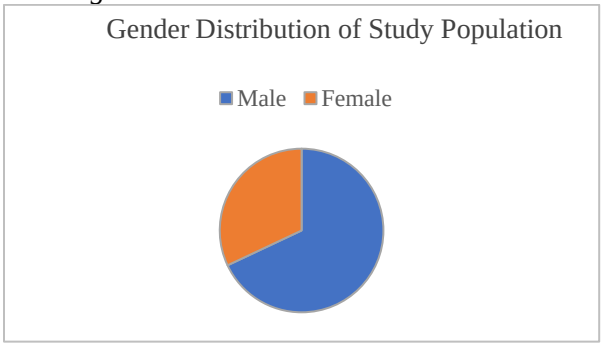
RESULTS

Two hundred ninety-eight patients received at least

one DES throughout the research period. ISR was identified in 50 individuals (16.77%). Thus, 50 patients who fulfilled the inclusion criteria were included in the study. Males comprised 68% of the study population, while females comprised 32% of the study population, as shown in Figure 1.

Figure 1

Showing the Gender Distribution



2% of the study population presented with STEMI, 22% with NSTEMI, 24% with UA, and 52% with non-ACS (Table 1).

Table 1

Presentation of the Study Population

Variable		N=50 N, %
Age in years	63.54 ± 15.69	
ACS	STEMI	1 (2)
	NSTEMI	11(22)
	UA	12(24)
Non-ACS		26(52)

Among all the patients that had ISR, diabetes and hypertension were the most common comorbidities found in the study population. Diabetes was present in 62% of the individuals, while hypertension was present in 66% of the study population (Figure 2). Other details of comorbidities in the study population are shown in Table 2.

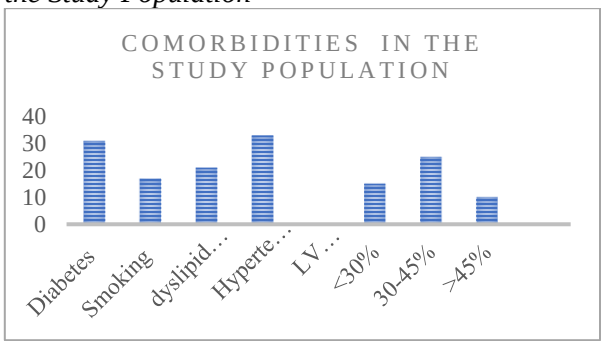
Table 2

Comorbidities in the Study Population

Variable	N, %
Diabetes	31(62)
Smoking	17(34)
dyslipidemia	21(42)
Hypertension	33(66)
LV function	
<30%	15(30)
30-45%	25(50)
>45%	10(20)

Figure 2

Shows the Comorbidities and Ejection Fraction of the Study Population



Following coronary angiography, it was discovered that the frequency of ISR was 11(22%) in patients with Xlimus sirolimus stent, 10(20%) with Xience (everolimus-eluting stent), 13(26%) with Ultimate (sirolimus-eluting stent), and 16(32%) with Biomatrix stent.

Table 3

Prevalence of ISR in different DES

Variable	N, %	P value
Xience	10(20)	0.42
Xlimus	11(22)	
Biomatrix	16(32)	
Ultimate	13(26)	

During the research period, 28 patients with DES ISR who met the inclusion criteria received revascularisation with DEB. There were no acute post-procedural challenges, such as reflow or dissection. One patient died during a hospital stay due to cardiogenic shock. No individual experienced MACE; however, four patients continued to have complaints of angina and were managed medically.

After a median of 18 months of follow-up, eight patients remained symptomatic, with 4 developing MACE, one resulting in cardiac death, and 3 requiring revascularization. Thus, the overall MACE rate was 21%. There were two fatalities from non-cardiac causes (table 4).

Table 4

Complications of Treatment with DEB

Variable	In hospital rates N=28	At follow up N=27
Bleeding	1(3.5)	-
Angina	4(14.2)	8(29.6)

symptoms		
Post-procedure fatality		
Cardiac	1(3.5)	1(3.7)
Non cardiac	0	2(7.4)
CABG required	-	3(11.1)
Re PTCA required	-	-

DISCUSSION

Our investigation was carried out to ascertain the incidence and frequency of ISR in various drug-eluting stents that were presented to our institution, regardless of their medical conditions and clinical manifestations. We also looked into the management of these DES ISRs and the efficacy of the treatment.

Stent thrombosis and restenosis are among the most significant issues following stent deployment. (10). In contrast to ISR, which typically manifests as chronic or unstable angina (11)Stent thrombosis typically presents as abrupt, intense chest pain that is accompanied by myocardial infarction (MI) in the stented arterial area. (1). One of the most significant clinical issues after stent deployments with bare metal stents was the frequency of stent restenosis, which occurred in 10–30% of procedures. (12).

However, besides the stent design and polymer, which are the primary causes of restenosis, there are a few more risk factors in-stent restenosis. These risk variables can be subdivided into patient-related risk factors such as diabetes mellitus, male gender, genetics, hypertension, and a high cholesterol level or factors such as stent length, vascular diameter, ostial lesions, and CTO. (13, 14).

In our study, patients with ISR had a high prevalence of diabetes and hypertension. Hypertension and diabetes are risk factors for ISR, as documented in previous research. (15, 16)Our study's results align with those of previous research. In our research, males comprised 68% of the study population. This is due to prior research, which found that 66.7% of patients who presented with ISR following angioplasty were male. (17). All these results are in line with the previous research published on ISR. (13, 17).

Following structural and design changes, the frequency of ISR in newer-generation stents has been much lower. The next-generation Everolimus eluting stents are more beneficial than the first-generation Paclitaxel-eluting stent (PES) in terms of ISR and repeated revascularisation, according to several randomised studies. (18). According to one research, patients who first appear with troponin-positive acute coronary syndrome may be at risk for adverse events that may occur following ISR treatment. (19). On the other hand, Steinberg et al.'s further observational analysis revealed no variation in adverse events following the procedure. (20).

The production of DEBs has proven to be one of the most effective techniques for treating ISR lesions. The paclitaxel-eluting balloon and an uncoated balloon were tested for the management of coronary ISR in the PACCOCATH ISR I trial, the first clinical study for DEB. A significant reduction in late lumen loss was observed in the coated balloon groups following the six-month post-angiography follow-up. (21). The PACCOCATH ISR I and II trials were combined to obtain a bigger sample size and longer follow-up duration. The methods for both studies were the same. These findings corroborated the earlier findings, showing that the coated-balloon group had reduced rates of MACE and binary restenosis up to two years later. (22).

The question, though, was whether the DEB was safer and more effective than the DES, the treatment of choice for lesions with ISR. The PEPCAD II study solved this question by testing the SeQuent Please paclitaxel-eluting balloon with the Taxus Liberté paclitaxel-eluting stent in lesions with ISR. The trial revealed that the DEB group had a reduced rate of late lumen loss and a lower binary restenosis rate at the six-month follow-up (22). Therefore, in patients with ISR, the DEB was ideally as safe and effective as the DES. It should be noted that although patients with ISR in BMS were enrolled in the PEPCAD II trial,14 data regarding the involvement of DEB in DES-ISR are still being collected.

ISR in DES is recognised to be more challenging to treat, and further DES in such cases also has more significant risks of MACE and revascularization (23)A recent paper documents Latib et al.'s experience using SeQuent Please DEB to treat DES-ISR for bifurcating lesions, which shows promising results. (24)Additional data is available with a different DEB technology called DIOR, which was assessed by the multinational

centre in Spain, which examined the one-year results of ISR in both BMS and DES. (25). Results were positive in both groups, having a MACE incidence of 16.7%; nevertheless, the DES group exhibited a non-significant tendency toward higher MACE at one year. Similarly, data from a broader multicenter registry on the application of Dior in ISR lesions in BMS and DES were published. Additionally, at 7.5 months of follow-up, their results showed an encouraging accumulated MACE rate of 11.5%.

The results of this study confirm that the DEB, among other cardiovascular risk factors, reduces the development of binary restenosis in individuals with diabetes, which is recognised to be a risk factor for developing ISR. Additionally, the patient's more complicated lesions may have contributed to the marginally higher MACE rate than in other registries.

There are various limitations to this investigation that need to be considered. Due to the small sample size, it might not fully capture all of the effects of DEB treatment for these patients. To properly determine DEBs' significance for this indication, however, well-designed trials with sufficient sample size are still needed as research into the drug's potential for treating DES-ISR lesions is still in its early stages. Furthermore, follow-up angiography was not performed on our patients to ascertain whether the treatment succeeded. As a result, it is possible that the MACE-causing lesion in those patients who died had other causes other than the DEB-treated lesion. However, this follow-up required more resources than this study could provide.

CONCLUSION

ISR frequently presents as angina in every new generation DES. Between the second and third-generation DES, there was no statistically significant difference with regard to ISR.ISR could benefit from DEB technology, especially for DES. Our experience emphasizes the need for additional research, such as randomised trials involving different patient groups. However, more investigation is needed to determine their effectiveness in this role.

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