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Incidence and Predictors of Outcome in the Treatment of In-Stent Restenosis with Drug-Eluting Balloons

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Author`s Contribution

[1,3]Conception, synthesis, planning of research, and writing of the manuscript/Data Collection, Final Approval of the study to be published, [2,5]Active participation in methodology, interpretation, and discussion, review of the manuscript,[4,6]data entries, and statistical data analysis, Literature Review

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ABSTRACT

Objective: To evaluate the incidence of major adverse cardiac events (MACE) and identify clinical and procedural predictors of outcomes in patients undergoing DEB treatment for ISR.

Methodology: This was a retrospective cohort study conducted at Pakistan Institute of Medical science, Islamabad, during study period July 2022 to July 2023. All patients with age ≥18 years, angiographically confirmed restenosis were included. Follow-up was conducted for 12 months post-intervention. We conducted multivariate analyses to explore the association between each predictor (e.g., age, comorbidities, procedural characteristics) and the outcomes (e.g., major adverse cardiac events, re-stenosis) employing logistic regression. SPSS v 29 was used for data analysis.

Results: A total of 264 patients were included in the study majority male (73.86%), with a mean age of 61.42± 9.74 years. Procedural success of 99.24% was achieved, and restenosis occurred in 10.6% of patients within the 12-month. The cumulative incidence of MACE was 8% at 12 months with diabetes mellitus (HR: 1.9, 95% CI: 1.1-3.2, p<0.01), stent length >20 mm (HR: 1.7, 95% CI: 1.0-2.8, p<0.05), and suboptimal stent expansion (HR: 2.6, 95% CI: 1.7-4.8, p<0.01). Moreover, age more than 65 years and multiple vessel disease were significant predictors of MACE. KM analysis revealed significantly higher ISR and lower MACE-free survival in patients with DM and longer stent (p<0.01 and p<0.05, respectively).

Conclusion: In conclusion, the use of DEBs in the treatment of ISR shows a good procedural success rate along with a controllable restenosis recurrence rate. Significant predictors of unfavorable outcomes, such as diabetes mellitus, stent length, and poor stent expansion, were identified

Keywords: Coronary artery disease, In-stent restenosis drug-eluting balloons, percutaneous coronary intervention.

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Introduction

In-stent restenosis (ISR), characterized by the re-narrowing of an earlier stented coronary artery represents a substantial therapeutic issue in the field of Interventional cardiology. [1, 2] ISR occurs commonly in patients with coronary artery stenting, with an estimated prevalence of 5%. [3] It is mainly caused by neointimal hyperplasia, and associated with proliferative response of vascular smooth muscle cells which keeps the blockage at the site of stent implantation from reforming.[4, 5] The efficacy of stent implantation is greatly challenged by this shift over the

long run and requires further medical attention. Moreover, the pathophysiological outcomes of ISR and its ability to cause persistent angina, myocardial infarction (MI), and revascularization episodes make it a significant clinical concern. [6-8] These recurrent cardiovascular episodes are coming at a higher cost to healthcare system all over the world and specially to developing countries like Pakistan. The burden of ISR emphasizes an immense need for efficient and cost-effective treatment strategies to improve patient outcomes. [7, 8]

Standard therapies involve plain old ballon angioplasty (POBA), balloon cutting or scoring, and repeat stenting with drug-eluting stents (DES). [9-11] POBA allowed the percutaneous involvement of stenosed coronary arteries by pumping air into a ballon at blockage site to bring back the blood, although the efficacy is limited by elastic recoil and blood flow restricting dissections.[9] Cutting and scoring balloons endeavor better outcomes than POBA by making more perfect cuts in the arteries but this procedure is also exposed to certain limitations.[11] DES repeat stenting is implanting a fresh stent with antiproliferative agents to prevent additional neointimal development.[10] Regardless of progress, these treatments continue to confront challenges with high chance of recurrence and outcomes like stent thrombosis. [12]

In this regard, drug-eluting balloons (DEBs) have emerged as a promising substitute to treat ISR. DEBs provide homogenous and high concentration dose of antiproliferative agents to the vessel walls during balloon inflation that reduce the inflammation without leaving a permanent implant.[13] The 2014 European Society of Cardiology Myocardial Revascularization guidelines acknowledged this benefit and suggested that DEBs be used to treat BMS ISR in addition to DES. DEBs reduce the chance of stent thrombosis and restenosis recurrence since they do not require a permanent scaffold inside the artery.[14]

Addressing several critical gaps in current clinical knowledge and practice, this study investigates the efficacy, safety, and predictive factors associated with drug-eluting balloons (DEB) in the treatment of in-stent restenosis (ISR). Despite advancements in drug-eluting stents (DES), ISR remains a significant challenge, necessitating effective alternative treatments like DEB. Evaluating real-world incidence and outcomes of DEB, particularly in terms of clinical predictors of treatment success or failure, aims to optimize patient selection and treatment strategies, potentially improving clinical outcomes and guiding future ISR management guidelines and practices.

Methodology

This was a retrospective cohort study conducted at Pakistan Institute of Medical science, Islamabad, during study period July 2022 to July 2023. Patients included in the study were those who underwent coronary stenting with DEBs for ISR of previously implanted drug-eluting stents (DES) or bare-metal stents (BMS). All patients with age ≥18 years, angiographically confirmed restenosis were included. Those with a new lesion in the same vessel, concomitant use of additional stents during the procedure, and incomplete clinical follow-up were excluded from the study.

Outcome variables were assessed by defining primary outcomes as major adverse cardiac events (MACE), restenosis. MACE was defined as a composite of cardiovascular death, myocardial infarction, and need for urgent revascularization. Restenosis was defined as the recurrence of stenosis of the treated vessel segment, confirmed angiographically during follow-up.

All data were extracted from electronic medical records and cath lab databases. Data on baseline characteristics included age, gender, history of hyperlipidemia, diabetes mellitus, hypertension, and previous cardiovascular events like myocardial infarction, stroke. Procedural data includes details of the initial stent implantation, characteristics of ISR, and specifics of the DEB intervention.

Patients were followed clinically and angiographically for 12 months post-intervention, and thereafter annually or as clinically indicated. Follow-up data were obtained through clinic visits, telephone interviews, and review of medical records. Angiographic follow-up included QCA to assess ISR recurrence and procedural success.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of PIMS Islamabad. Informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

Descriptive statistics were used to summarize baseline characteristics and procedural data. Continuous variables were expressed as mean ± standard deviation, categorical variables were presented as frequencies and percentages. Kaplan-Meier survival analysis was employed to estimate the incidence of MACE over time, with comparisons made

using the log-rank test. Cox proportional hazards regression models were used to identify independent predictors of MACE, incorporating variables with a p-value <0.1 in univariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

Results

Between January 2015 and December 2020, a total of 264 patients who had previously undergone coronary stenting and subsequently developed in-stent restenosis (ISR) were enrolled. The mean age was 61.42 ± 9.74 years; 70% were male. Common comorbidities included hypertension 201(76.13%), diabetes mellitus 105(39.77%), and hyperlipidemia 145(54.92%). A history of previous myocardial infarction was present in 52(19.69%) of patients, and majority 130(49.24%) had only one stent. (Table I)

Table I: Baseline Characteristics of the Study Population.

Characteristic	Frequency	Percentage
Age (Mean±SD)	61.42 ± 9.74 years	
Male	195	73.86
Hypertension	201	76.13
Hyperlipidemia	145	54.92
Diabetes mellitus	105	39.77
Previous MI	52	19.69
Number of Stents		
One stent	130	49.24
Two stents	97	36.74
Three stents	37	14.01

Majority 138(52.27%) were in type 1 Mehran classification, The mean stent length was 22.7 ± 3.7 mm, and the mean stent diameter was 3.4 ± 0.6 mm. Pre-dilatation was performed in 212(80.30%) of cases. The mean balloon inflation pressure was 11.8 ± 3.1 atm, with an average inflation time of 57 seconds. Procedural success, defined as residual stenosis <30% without major complications, was achieved in 262(99.24%) of cases. (Table II)

Table II: Procedural Characteristics and Outcomes.

Characteristics	Value
Mehran classification	
Type I, n (%)	138(52.27)
Type II, n (%)	75(28.40)
Type III, n (%)	41(15.53)
Type IV, n (%)	10(3.78)
Mean stent length (mm)	22.7 ± 3.7
Mean stent diameter (mm)	3.4 ± 0.6
Mean balloon inflation pressure, atm	11.8 ± 3.1
Pre-dilatation, n (%)	212 (80.30%)
Mean inflation time (sec)	57
Procedural success, n (%)	262 (99.24%)

Of the 264 patients treated with drug-eluting balloons (DEBs), 28(10.60%) patients experienced recurrent restenosis within the 12-month follow-up period. During a median follow-up of 12 months, corresponding to an incidence rate of 10 restenosis cases per 100 patient-years. The cumulative incidence of MACE, including myocardial infarction, stroke, and cardiovascular death, was 34(12.87%) at 12 months. Figure 1

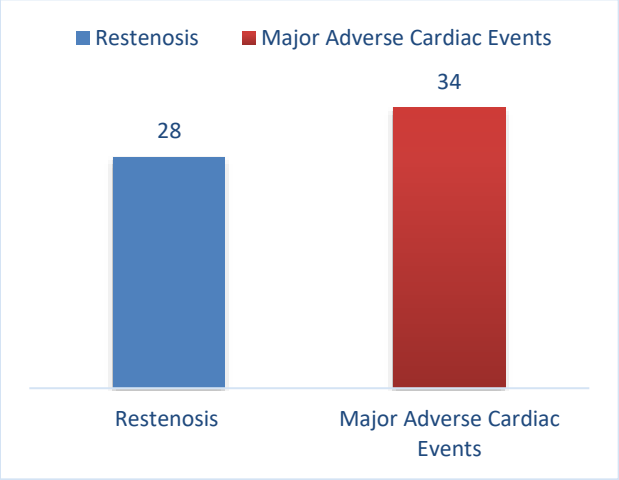

Figure 1: Incidence of Primary Outcomes.

The cumulative incidence of MACE, including myocardial infarction, stroke, and cardiovascular death, was 12% at 12 months. Multivariable analysis identified diabetes mellitus (HR: 1.9, 95% CI: 1.1-3.2, p<0.01), stent length >20 mm (HR: 1.7, 95% CI: 1.0-2.8, p<0.05), and suboptimal stent expansion (HR: 2.6, 95% CI: 1.7-4.8, p<0.01) as significant predictors for restenosis. Additionally, age >65 years and the presence of multi-vessel disease were significant predictors of MACE. (Table III)

Table III: Predictors of ISR and MACE.

Predictor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Restenosis			
Diabetes Mellitus	1.9	1.1-3.2	<0.01
Stent length >20 mm	1.7	1.0-2.8	<0.05
Suboptimal stent expansion	2.6	1.7-4.8	<0.01
MACE			
Age >65 years	1.9	1.3-2.7	<0.05
Multi-vessel disease	2.2	1.4-3.8	<0.05

The Kaplan-Meier analysis for restenosis incidence and MACE-free survival reveals significant differences based on the presence of diabetes mellitus and stent length. Patients with diabetes mellitus exhibited a markedly higher incidence of ISR at 14% compared to 7% in non-diabetic patients, with this difference being statistically

significant ($p < 0.01$). Additionally, the MACE-free survival rate for diabetic patients was significantly lower at 71% compared to 89% for non-diabetic patients ($p < 0.01$). Similarly, patients with stent lengths greater than 20 mm experienced a higher ISR incidence of 13% versus 6% for those with stent lengths of 20 mm or less, with a p-value of < 0.05. The MACE-free survival for patients with longer stents was also significantly lower at 75% compared to 88% for those with shorter stents ($p < 0.05$). (Table V)

Table V: Kaplan-Meier Analysis for ISR and MACE.

Group	Restenosis Incidence (%)	p-value	MACE-Free Survival (%)	p-value
Diabetes Mellitus	14	<0.01	71	<0.01
No Diabetes Mellitus	7		89	
Stent length >20 mm	13	<0.05	75	<0.05
Stent length ≤20 mm	6		88	

Discussion

This real-world, all-comers study investigates the incidence and predictors of outcomes in the treatment of ISR using DEBs. Conducted on patients who had previously undergone coronary stenting, our study discovered a recurrence rate of 10.6% and an incidence of MACE of 8% in 12 months follow-up. Procedural success was high, with an outcome rate of 99.2%. Significant predictors of ISR included diabetes mellitus, stent length more than 20 mm, and suboptimal stent expansion, while MACE was predicted by age more than 65 years and multivessel disease. Kaplan-Meier analysis indicated that patients with diabetes and longer stents had shorter MACE-free survival and higher rates of restenosis.

Markedly, 19.69% of patients had a history of MI, with nearly half having received a single stent. These findings are consistent with those observed in literature on ISR treatment.[2, 15] This study found a higher prevalence of hypertension and a history of MI, whereas one research reported a higher prevalence of diabetes and MI history.[15]

The success rate, defined as achieving residual stenosis of less than 30% without significant complications, was exceptionally high, underscoring the effectiveness of DEBs in achieving immediate procedural goals. This high success rate aligns with other studies demonstrating the technical feasibility of DEBs in treating ISR. Alfonso et al. demonstrate that DEBs significantly decrease the incidence of ISR, with current evidence it offer the best clinical and angiographic results.[16] Local study by Farza et al[15] showed that DEBs the five year MACE was almost 50% which was higher than our study. Moreover, Dinc et al[17] conclude that DEBs are more preferred over other interventions, due to less cases of restenosis in follow-up.

During follow-up there were significant increases in the cumulative incidence of MACE, which included MI, stroke, and cardiovascular mortality. Although the study only examined one-year outcomes, it performed well in terms of mortality (12.87%), with a reasonable MACE rate. Our study's mortality rate was slightly higher than that reported in comparable one-year trials. Nagasaka et al.[18] showed mortality of 3.8% in his study, however the mortality in study by Qi wu [19] was similar to our study, highlighting the ongoing challenge in managing ISR.

Current evidence suggests DEBs offer the best clinical and angiographic results, yet further studies are needed to refine and tailor therapeutic strategies to improve outcomes amidst a rapidly evolving field. Multivariable analysis identified stent length >20 mm, poor stent expansion, and diabetes mellitus as significant predictors of restenosis. Similarly, age >65 years and multivessel disease were significant predictors of MACE, consistent with previous studies.[20, 21] The comparatively lower incidence of MACE and recurrent restenosis in this study may be attributed to enhanced procedural methods and advancements in DEB technology.

Regarding the stent length and diabetes, the survival analysis showed significant differences in the outcomes. Higher incidence of ISR and shorter MACE-free survival in the diabetic group suggesting that diabetic patients are at higher risk as compared to non-diabetic patients. Likewise, patients with longer stent patients, showing greater ISR rates with lower MACE-free survival. These findings are consistent with previous studies which demonstrated that diabetes mellitus significantly increases ISR risk along with adverse cardiovascular events after stenting. [6, 16, 22]

The study confirmed that the key determinants of MACE in our population was past medical history. Moreover, this study highlights the potential of DEBs as a therapeutic option for ISR treatment, particularly for patients with diabetes and longer stents, highlighting the need for optimal procedures and strategies to improve long-term outcomes.

Conclusion

In conclusion, the use of DEBs in the treatment of ISR shows a good procedural success rate along with a controllable restenosis recurrence rate. Significant predictors of unfavorable outcomes, such as diabetes mellitus, stent length, and poor stent expansion, were identified. This study determines that the use of DEBs for treatment of ISR is safe. Moreover, this study highlights the necessity of customized treatment plans to manage the risks associated to patient comorbidities and stent attributes. Future research should focus on additional treatments that can boost DEB efficacy and enhance long-term clinical outcomes in ISR patients.

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