In-stent restenosis of drug-eluting stents in patients with diabetes mellitus: Clinical presentation, angiographic features, and outcomes

Ganesh Paramasivam, Tom Devasia, Ashwal Jayaram, Abdul Razak, M. Sudhakar Rao, Rajesh Vijayvergiya[1], Krishnananda Nayak[2]

Department of Cardiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal; Karnataka-*India*
[1]Department of Cardiology, Postgraduate Institute of Medical Education and Research (PGIMER); Chandigarh-*India*
[2]Department of Cardiovascular Technology, School of Allied Health Sciences,
Manipal Academy of Higher Education, Manipal; Karnataka-*India*

Abstract

Objective: Diabetes mellitus (DM) is a risk factor for developing in-stent restenosis (ISR) following percutaneous coronary intervention (PCI). This study aimed to examine the presentation and outcomes of drug-eluting stent (DES) ISR in diabetics.

Methods: This retrospective study included consecutive patients with clinical DES-ISR, who were hospitalized between January 2013 and December 2017 and who were grouped based on the presence or absence of DM. Clinical, angiographic features and 1-year outcomes [composite of death, myocardial infarction (MI), and repeat-target lesion revascularization] were compared.

Results: Baseline characteristics of the DM group (n=109) were comparable to the non-DM group (n=82), except for the higher prevalence of hypertension and dyslipidemia in the former (60.6% vs. 46.3%, p=0.050; 74.4% vs. 57.8%, p=0.034, respectively). Clinical presentation was similar in both groups [acute coronary syndrome (ACS): 62.4% vs. 61%, p=0.843; MI: 34.9% vs. 34.1%, p=0.918). Diabetics had a higher prevalence of stent-edge restenosis (20.3% vs. 9.2%, p=0.019). The treatment strategy was similar in both groups with 52.3% in the DM group and 57.3% in the non-DM group undergoing PCI (p=0.513). One-year outcomes of the DM group were not different from those of the non-DM group (14.7% vs. 17.1%, p=0.683). Age [hazard ratio (HR), 1.05; 95% confidence interval (CI), 1.01–1.10; p=0.017], MI presentation (HR, 2.34; 95% CI, 1.14–4.80; p=0.020), and chronic kidney disease (CKD: HR, 2.82; 95% CI, 1.21–6.58; p=0.016) were predictors of poor outcomes.

Conclusion: Stent-edge restenosis is more common in diabetics. Clinical presentation and 1-year outcomes following DES-ISR are similar in diabetics and non-diabetics. Age, MI presentation, CKD, and not DM were predictors of poor outcomes following DES-ISR. *(Anatol J Cardiol 2020; 23: 28-34)*

Keywords: coronary restenosis, drug-eluting stent, diabetes mellitus, in-stent restenosis, percutaneous coronary intervention, percutaneous transluminal coronary angioplasty

Introduction

In-stent restenosis (ISR) is the bane of percutaneous coronary intervention (PCI) (1). Although drug-eluting stents (DES) have reduced the incidence of ISR, it continues to be a significant problem affecting 5%–10% of the patients undergoing PCI (2).

Patients with diabetes mellitus (DM) are at higher risk of developing ISR due to excess neointimal hyperplasia, hypercoagulability, increased inflammatory response, endothelial dysfunction, and presence of comorbidities (3). In the bare-metal stent (BMS) era, diabetes was an independent risk factor for both ISR and major adverse cardiac events (MACE) following PCI (4). It is unclear whether diabetics are at increased risk of developing ISR in the DES era. Few studies suggest that diabetes is no longer associated with ISR following DES implantation, while others found it to be associated with an increased ISR risk (3, 5, 6). However, poorer clinical outcomes have been reported in diabetics following PCI compared to their non-diabetic counterparts, even in the DES era (7). Whether patients with diabetes who develop DES-ISR fare poorly compared to their non-diabetic counterparts is unknown because data are scarce regarding the clinical presentation and outcomes in diabetic patients with DES-ISR (8). Few available studies in this area have compared one PCI modality over the other in a clinical trial setting, which is not reflective of the real-world situation (9-11).

We compared the clinical presentation, angiographic features, and outcomes of DES-ISR among patients with and without DM.

Address for correspondence: Tom Devasia, MD, Department of Cardiology, Kasturba Medical College,
Manipal Academy of Higher Education; 576104, Karnataka-*India*
Phone: +0820-2922353 E-mail: gt.cardiology@gmail.com
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Methods

Study population and design

This study was conducted in a tertiary care hospital in South India. All the patients presenting with clinical ISR of DES between January 2013 and December 2017 were included in this retrospective cohort study and grouped according to the presence or absence of DM. The study protocol was approved by the Institutional Ethics Committee and was registered with the Clinical Trials Registry–India (Reg. No. CTRI/2018/10/016181).

Demographic and clinical characteristics, investigations including biochemical test results, and electrocardiographic and echocardiographic findings were noted from patients' medical records. Two independent cardiologists reviewed the angiographic images to confirm the presence of ISR and to determine the type of ISR (according to the Mehran classification) (12). Details pertaining to the treatment of culprit ISR lesion, including technical details of interventional procedures, were recorded.

Study definitions

ISR was defined as the presence of >50% diameter stenosis on angiography at the stent site or at its edges (adjacent 5 mm segments) (13). Clinical ISR was defined as the presence of symptoms attributable to the ISR lesion.

Patients were considered to be diabetic if they were previously diagnosed or were under treatment for DM or if glycosylated hemoglobin level was ≥6.5% during the index hospitalization. Fasting blood glucose during index hospitalization was not used for diagnosing diabetes, as stress hyperglycemia can lead to false-positive diagnoses.

Clinical presentation at index hospitalization during which ISR was first diagnosed was classified into acute coronary syndrome (ACS) and non-ACS. The ACS group included patients with myocardial infarction (MI) and unstable angina (UA). Non-ACS group included patients presenting with stable angina or silent ischemia.

MI was defined according to the universal definition and was categorized into STEMI (ST-elevation myocardial infarction), when characterized by the ST-segment elevation or new-onset left bundle branch block, and NSTEMI (non-ST elevation myocardial infarction) when there was a rise or fall in cardiac biomarkers (cardiac troponin T) without ST-segment elevation (14).

Stable angina was defined as typical chest discomfort brought upon by physical exertion and relieved by rest and/or nitrates. UA was defined as a recent onset or worsening of typical chest pain, chest pain occurring at rest, or chest pain lasting >20 minutes, with or without dynamic ST-segment changes on electrocardiography and without elevation of cardiac biomarkers. Abnormality on stress tests (the treadmill test or dobutamine stress echocardiography) without typical symptoms was labeled as silent ischemia (15).

Chronic kidney disease was defined according to the Kidney Disease: Improving Global Outcomes 2012 guidelines (16). Congestive cardiac failure was defined as the evidence of fluid retention from cardiac causes. Stent thrombosis, definite or probable, was defined according to criteria from the Academic Research Consortium (17).

Outcome definitions

The primary outcome studied was a composite of all-cause mortality and major adverse cardiac events (MACE) after index hospitalization. MACE included MI and repeat target-lesion revascularization (TLR). MI that led to index hospitalization and the first TLR carried out for index ISR lesion were not included in the cumulative MACE. Only repeat (or second) TLR that occurred during the follow-up was considered as a MACE for the purpose of this study. All deaths were considered cardiac unless another documented cause was found.

Follow-up

Clinical follow-up data were obtained from patients' medical records for a period of 1 year after index hospitalization to determine the occurrence of an adverse event(s). In patients for whom such data were not available from hospital records, follow-up was conducted by telephonic contact. All adverse events were adjudicated by interventional cardiologists who were blinded to the study objectives.

Study objectives

The main objective of this study was to compare the clinical and angiographic characteristics and outcomes of DES-ISR among patients with and without DM. The secondary objective was to identify the predictors of poor outcomes in patients with DES-ISR.

Statistical analysis

Categorical variables were summarized using frequencies (%). The mean±standard deviation was used for continuous variables. Normality was assessed for continuous data using the Kolmogorov–Smirnov test. The independent samples t-test was used for continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The Kaplan–Meier method and the log-rank test were used to compare survival (time-to-event) curves of patients with and without DM. The Cox regression analysis was used to calculate the hazard ratios for predictors of clinical outcomes following DES-ISR. A p-value <0.05 was taken as an indicator of statistical significance. A statistical analysis was carried out using the SPSS Inc., Version 16.0 (Chicago, Illinois, USA).

Results

Clinical and angiographic characteristics

This study included 109 patients with DM and 82 patients without DM who presented with clinical ISR of DES (a total of 191

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patients with 210 culprit ISR lesions). Approximately, 18,771 diagnostic angiograms were done during the study period, of which 1,318 angiographies were those of patients with a previous PTCA procedure. Therefore, roughly 14.5% (191 study patients out of 1,318) had clinical ISR where an ISR lesion was found to be the culprit. Although this "restenosis rate" is higher than that reported with DES (5%–10%), it should be noted that the decision for repeat angiogram in a patient with previous PTCA was based on clinical suspicion and as per treating physician's discretion (2). A practice of doing routine check angiograms after a fixed period to look for ISR is not followed in our center.

Patient characteristics at index hospitalization are presented in Table 1. Patients in both groups were similar with respect to age, gender, tobacco consumption, co-existing illness, left ventricular function, and the New York Heart Association class. Patients with DM had a higher prevalence of hypertension and lipid abnormalities compared to non-diabetics, despite similar rates of statin therapy.

Clinical presentation of DES-ISR was similar among both diabetics and non-diabetics with ACS being the most common presentation mode in both groups. One-third of the patients in both the groups presented with MI (Table 1).

Angiographic features, treatment characteristics, and details of interventional procedures are presented in Table 2. A focal ISR lesion (Mehran Type 1) was the most common lesion type in both groups. Diabetics had higher prevalence of Type 1B lesions (stent-edge restenosis) and a lower prevalence of Type 1C lesions compared to non-diabetics [25 (20.3%) vs. 8 (9.2%), p=0.019; and 37 (30.1%) vs. 36 (41.4%), p=0.039, respectively].

Patients with DM had a trend toward a higher prevalence of triple-vessel disease (DM vs. non-DM: 32.1% vs. 20.7%, p=0.080). Both groups were similar with respect to vessels affected by ISR, the ISR location, and treatment received. PCI was the most common treatment modality in both groups, and more than two-thirds of patients undergoing PCI received a new DES (Table 2).

Data on three more variables (length and diameter of previous stent in which ISR developed and time to ISR) were available only in 136 study patients. The average length of the previous stents was 23.4±11.1 mm and 21.5±10.5 mm, respectively, in diabetic and non-diabetic groups (p=0.854). An average diameter of these stents was 2.81±0.3 and 2.97±0.3 mm, respectively, in diabetics and non-diabetics (p=0.370). The mean time to restenosis in diabetics and non-diabetics was 26.7±8.7 months and 32.2±6.4 months, respectively (p=0.431). Although this suggests that diabetics developed ISR earlier and had received longer stents with smaller diameters during their initial PCI, the differences were not statistically significant.

Effect of diabetes on clinical outcomes

There was no significant difference in the occurrence of the primary composite outcome between the DM group and the non-DM group at the end of the 1-year follow-up period (14.7% vs. 17.1%, respectively, p=0.653). The Kaplan–Meier analysis of 1-year outcomes in DM and non-DM groups is shown in Figure 1. Both groups had comparable rates of all-cause mortality (5.5% vs. 6.1%, p=0.862) and MI (6.4% vs. 4.9%, p=0.650). The DM group had a lower rate of re-TLR compared to the non-DM

Table 1. Patient characteristics at first clinical in-stent restenosis presentation

Parameter	DM group (n=109)	Non-DM group (n=82)	*P*-value
Demographics			
Age	60.7±9.3	61.8±10.8	0.464
Men	90 (82.6%)	65 (79.3%)	0.564
BMI	23.3±3.7	23.6±3.1	0.690
Clinical characteristics			
Hypertension#	66 (60.6%)	38 (46.3%)	**0.050**
Chronic kidney disease	12 (11.0%)	9 (11.0%)	0.994
Acute kidney injury	20 (18.3%)	12 (14.6%)	0.496
Dyslipidemia*	61 (74.4%)	37 (57.8%)	**0.034**
Current tobacco use	21 (19.3%)	18 (22.0%)	0.649
CCF	21 (19.3%)	13 (15.9%)	0.542
NYHA 3, 4	9 (8.3%)	11 (13.4%)	0.249
LVEF	52.0±11.1	53.5±10.3	0.325
Previous MI	57 (52.3%)	43 (52.4%)	0.984
Previous CABG	10 (9.2%)	4 (4.9%)	0.259
Statin therapy	96 (88.1%)	67 (81.7%)	0.218
Clinical presentation			
Non-ACS	41 (37.6%)	32 (39.0%)	0.843
ACS	68 (62.4%)	50 (61.0%)	
Unstable angina	30 (27.5%)	22 (26.8%)	
MI	38 (34.9%)	28 (34.1%)	
NSTEMI	30 (27.5%)	22 (26.8%)	
STEMI	8 (7.3%)	6 (7.3%)	
Silent ischemia	14 (12.9%)	8 (9.8%)	0.398
Lab parameters			
HbA1c	8.2±1.4	5.8±0.4	**<0.001**
FBS	176±70	104±20	**<0.001**
Lipid profile* (mg/dL)			
Total cholesterol	143±44	148±39	0.450
LDL	78±37	83±33	0.437
HDL	38±11	42±12	0.063
Triglycerides	139±75	119±64	0.088

*Dyslipidemia defined as total cholesterol >250 mg/dL, LDL cholesterol >130 mg/dL, HDL cholesterol <40 mg/dL (<50 mg/dL for women) in the fasting state. Data available for 146 patients. #Blood pressure >140/90 mm Hg or the use of antihypertensive therapy. ACS - acute coronary syndrome; BMI - body mass index; CABG - coronary artery bypass grafting; CCF - congestive cardiac failure; HbA1c - glycosylated hemoglobin; LVEF - left ventricular ejection fraction; LDL - low-density lipoprotein; HDL - high-density lipoprotein; MI - myocardial infarction; NYHA - New York Heart Association

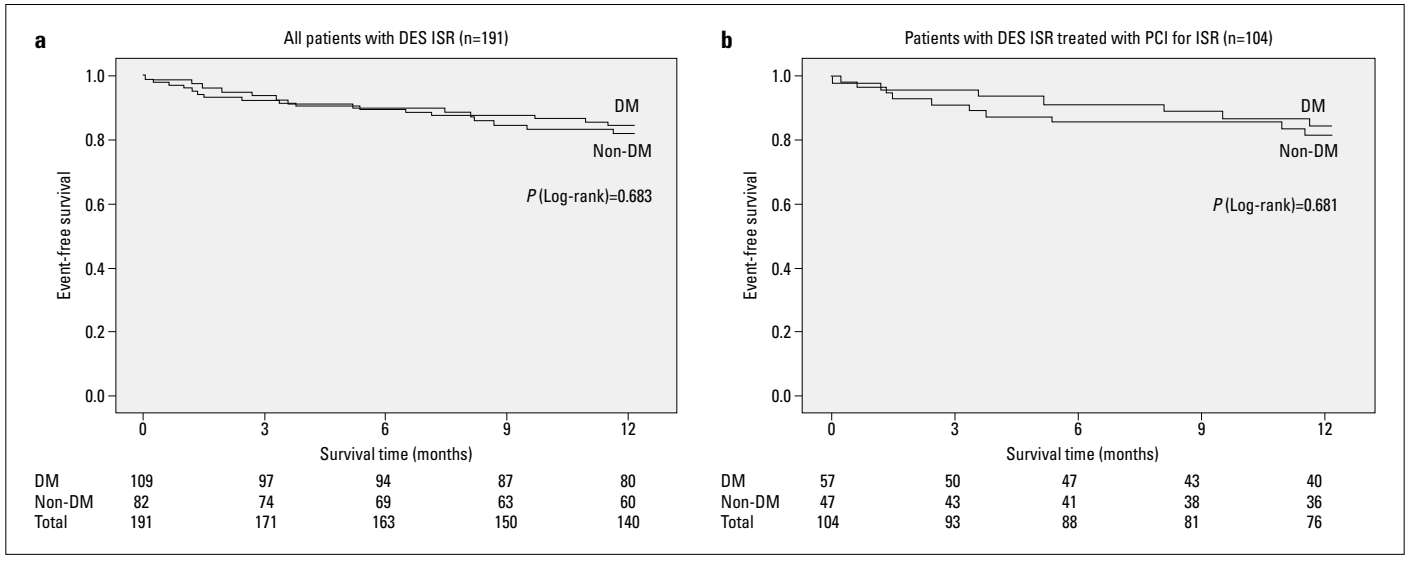

Figure 1. The Kaplan–Meier survival analysis of 1-year outcomes of DES-ISR according to the presence or absence of DM. (a) Entire DES-ISR cohort. (b) Subgroup of patients with DES-ISR treated with PCI for ISR lesion
DES - drug-eluting stent; DM - diabetes mellitus; ISR - in-stent restenosis; PCI - percutaneous coronary intervention

group (2.8% vs. 6.1%, p=0.253), but the difference was not statistically significant.

Although the patient number is low for subgroup analysis, we would like to report that there was no difference in outcomes with respect to the type of treatment received (PCI vs. medical therapy vs. CABG; p=0.928) or the type of PCI (DES vs. DEB vs. POBA; p=0.222).

Predictors of outcomes in DES-ISR

On the Cox regression analysis, DM did not appear to be associated with poor outcomes at the 1-year follow-up (Table 3). Among the other clinical and lesion-related parameters, the age, presentation with MI, and chronic kidney disease were associated with poor outcomes following DES-ISR in our study.

Discussion

To the best of our knowledge, our study is the first of its kind to compare the DES-ISR presentation and outcomes among patients with and without DM in a real-world scenario, irrespective of the type of treatment received for DES-ISR. The main findings of the study were the following: (1) Clinical presentation of DES-ISR is similar among patients with and without DM; (2) the ACS is the most common clinical presentation of DES-ISR in both groups; (3) a focal ISR lesion (Mehran Type 1) is the most common lesion type in both groups, but diabetics have a higher prevalence of Type 1B lesions (stent-edge restenosis) and a lower prevalence of Type 1C lesions compared to non-diabetics; (4) DM did not affect 1-year clinical outcomes following DES-ISR; (5) an advanced age, clinical presentation with MI, and the presence of chronic kidney disease were predictors of poor 1-year outcomes following DES-ISR.

Clinical presentation of DES-ISR in patients with DM

Although DES decreased the incidence of ISR, the propensity of ISR to present with ACS remained same in both the BMS and DES eras with up to 70% of patients presenting with ACS and 10%–20% with MI (18-21). Our study shows that patients with DM who develop DES-ISR have a clinical presentation very similar to those without DM. More than 60% of patients in both groups presented with ACS and nearly one-third of them presented with MI in our study. A recent study by Zhao et al. (8) also reported that diabetics and non-diabetics have a similar clinical presentation, but their study suggested that stable angina was the most common clinical presentation, which is at odds with most studies on DES-ISR. Patients with diabetes with *de novo* coronary artery disease are known to have a higher incidence of atypical symptoms, anginal equivalents, and silent ischemia, which may potentially lead to delayed presentation and higher chances of presenting with an ACS (22, 23). However, the presence of DM does not seem to have an effect on the manner of presentation of DES-ISR in our study. The prevalence of silent ischemia was similar in patients with and without DM in our study.

Angiographic characteristics of DES-ISR in patients with DM

In our study, focal restenosis (Mehran Type 1 lesion) was more common than non-focal ISR lesions in both patients with and without DM. This is in agreement with most previous studies, which found that focal restenosis is more common with DES compared to BMS restenosis, which presents more commonly with a diffuse pattern (24). DES, through its antiproliferative effects, seems to effectively reduce intimal hyperplasia and smooth muscle proliferation locally in the stented segment, even among patients with DM who are prone to excessive hyperplasia and restenosis.

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Table 2. Angiographic characteristics and treatment characteristics at first clinical in-stent restenosis presentation

Parameter ISR characteristics	DM group (n=123)	Non-DM group (n=87)	*P*-value
ISR type			0.866
I. Focal	78 (63.4%)	56 (64.4%)	
Type 1B	25 (20.3%)	8 (9.2%)	**0.019**
Type 1C	37 (30.1%)	36 (41.4%)	**0.039**
Type 1D	16 (13.0%)	12 (13.8%)	0.898
II. Diffuse	14 (11.4%)	9 (10.3%)	
III. Proliferative	7 (5.7%)	3 (3.4%)	
IV. Complete	24 (19.5%)	19 (21.8%)	
ISR vessel			0.583
Left anterior descending	70 (56.9%)	42 (48.3%)	
Left circumflex artery	25 (20.3%)	24 (27.6%)	
Right coronary artery	27 (22.0%)	20 (23.0%)	
Left main	1 (0.8%)	1 (1.1%)	
Proximal ISR location	70 (56.9%)	43 (49.4%)	0.284
Disease burden	**(n=109)**	**(n=82)**	0.195
Single-vessel disease	37 (33.9%)	35 (42.7%)	0.217
Double-vessel disease	37 (33.9%)	30 (36.6%)	0.705
Triple-vessel disease	35 (32.1%)	17 (20.7%)	0.080
Treatment	**(n=109)**	**(n=82)**	0.513
Medical therapy	20 (18.3%)	17 (20.7%)	
CABG	32 (29.4%)	18 (22.0%)	
PCI	57 (52.3%)	47 (57.3%)	
Details of PCI			
Procedural success	56 (98.2%)	45 (95.7%)	0.588
PCI type			0.427
POBA	14 (24.6%)	7 (14.9%)	
DCB	5 (8.8%)	6 (12.8%)	
New DES	38 (66.7%)	34 (72.3%)	
No. of stents	1.06±0.24	1.23±0.43	**0.051**
Stent length	29.4±8.5	30.0±13.3	0.828
Stent diameter	3.00±0.39	3.08±0.41	0.412
Adjunct devices			
Rotablation	1 (1.8%)	1 (2.1%)	1.000
Cutting or NC balloon	14 (24.6%)	10 (21.3%)	0.692
IVUS guidance	14 (24.6%)	11 (23.4%)	0.891

CABG - coronary artery bypass grafting; DCB - drug-coated balloon; DES - drug-eluting stent; IVUS - intravascular ultrasound; ISR - in-stent restenosis; NC - non-compliant; PCI - percutaneous coronary interventional; POBA - plain old balloon angioplasty

A notable finding in our study is the higher incidence of stent-edge restenosis (Mehran Type 1B lesion) among diabetics. Patients with diabetes have a smaller vessel caliber with longer and more diffuse *de novo* lesions compared to non-diabetics (25). This makes the initial PCI more challenging, especially with respect to choosing an appropriate stent length to cover the entire diseased segment leading to various degrees of geographical miss. This is especially true when visual estimation of lesion length based on angiographic images alone is used to decide the stent length (26). Often, the stent lands in a diseased segment, which then predisposes diabetic patients to the development of edge restenosis. It needs to be determined if intravascular imaging methods like intravascular ultrasound or optical coherence tomography may help overcome this issue in patients with DM.

Table 3. Predictors of 1-year clinical outcome following DES-ISR using Cox regression analysis

Variables	Hazard ratio	Lower 95% CI	Upper 95% CI	*P* value
Patient related				
Age	1.05	1.01	1.10	**0.017**
Female gender	1.39	0.60	3.24	0.446
Presentation with MI	2.34	1.14	4.80	**0.020**
Diabetes	0.86	0.42	1.77	0.684
Hypertension	1.08	0.52	2.22	0.836
Current tobacco use	1.52	0.68	3.42	0.309
Dyslipidemia	1.16	0.49	2.77	0.738
Chronic kidney disease	2.82	1.21	6.58	**0.016**
Lesion related				
Non-focal lesion	1.55	0.75	3.19	0.236
LAD involvement	1.26	0.61	2.62	0.531
Proximal ISR location	1.45	0.69	3.06	0.323

CABG - coronary artery bypass grafting; CI - confidence interval; ISR - in-stent restenosis; LAD - left anterior descending; LVEF - left ventricular ejection fraction; MI - myocardial infarction

Effect of DM on clinical outcomes in DES-ISR

Patients with DM in our study had a 1-year outcome (composite of death, MI, and re-TLR), similar to those without DM when both groups were managed with similar treatment strategies. Even in the subgroup managed with PCI, 1-year outcomes were similar in both diabetics and non-diabetics. A recent study comparing 2-year outcomes following the treatment of ISR with second-generation DES among diabetics and non-diabetics also reported that there is no difference between the two groups (8). It appears that DM is not a risk factor for poor outcomes following DES-ISR with currently available therapies. DM has been consistently found to be an independent risk factor for poor outcomes following PCI in several previous studies (4). Although the introduction of DES reduced the restenosis rates, diabetics as a group continued to experience poor outcomes (7). Because outcomes in those who develop restenosis are similar in diabet-

ics and non-diabetics, it suggests that the progression of disease elsewhere in the coronary tree and higher atherosclerotic burden along with comorbidities may be underlying poor outcomes among patients with DM. In this regard, the higher prevalence of triple-vessel disease, hypertension, and dyslipidemia among diabetics in our study supports this hypothesis.

Predictors of clinical outcomes in DES-ISR

We found that older age, chronic kidney disease, and presentation with MI were associated with worse 1-year outcomes following ISR. Lesion-related factors were not the markers of poor outcomes in our study. DES-ISR presenting with MI has been consistently reported to be a predictor of poor outcomes in many of the previous studies, emphasizing the need for a closer follow-up (18, 19). Similarly, several studies have shown that patients with chronic kidney disease are at a higher risk of developing restenosis because of a higher incidence of neoatherosclerosis, and have poorer outcomes following PCI (27, 28). A subset of patients with chronic kidney disease who develop DES-ISR is known to present with ACS and fare poorly despite treatment (18). Novel therapeutic options need to be explored to improve outcomes of patients with DES-ISR especially when one or more of these poor prognostic factors are present.

Study limitations

Because of the retrospective nature of this study, the results may have been affected by various confounding factors. Therefore, the findings of this study should be considered hypothesis generating.

The possibility of late stent thrombosis masquerading as ISR with MI cannot be excluded, despite the rigorous process of adjudication used. However, recent studies using intravascular imaging modalities have suggested that ISR and stent thrombosis may have a similar underlying pathophysiological basis and therefore may not be entirely distinct clinical entities as once believed.

The impact of the type of DES (first- vs. second-generation DES) on clinical presentation could not be compared because the type of DES received by study patients in their initial procedure (prior to the development of ISR) could not be ascertained in all patients because some of the patients had undergone initial PCI at a different hospital and presented to us for the first time with DES-ISR. However, in our country, a variety of stent types with various combinations of anti-proliferative drugs and polymers are available, which makes it difficult to segregate them into two or three groups for study purposes (29).

Treatment modalities were not compared because patients were treated at physician's discretion with either PCI, CABG, or medical management. Because re-TLR cannot occur in the latter two groups, re-TLR rates in our study are consequently lower. Further, the type of PCI (New DES, DCB or POBA) may also have influenced outcomes. However, we believe our study is representative of the entire spectrum of clinical ISR in the real-world situation where numerous factors affect treatment decisions and outcomes.

Conclusion

Patients with DM have a similar clinical presentation of DES-ISR compared to patients without DM, with ACS being the most common mode of presentation. Stent-edge restenosis is more common among diabetics. The presence of DM does not affect clinical outcomes at 1 year following contemporary treatment for DES-ISR. Higher age, presentation with MI and chronic kidney disease were predictors of poor outcomes at 1 year following DES-ISR.

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