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Article

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Abstract: Background Coronary artery disease (CAD) is a widely recognized cardiovascular disease that is considered the leading cause of death worldwide, affecting people on a global scale. Percutaneous coronary intervention (PCI), which involves procedures such as balloon angioplasty or stenting, plays an important role in opening blocked arteries and minimizing damage to the cardiac muscle. While the use of drug-eluting stents (DESs) has significantly reduced the occurrence of coronary restenosis, the problem of in-stent restenosis (ISR) continues to pose a significant clinical challenge. Gaining a deeper understanding of the clinical predictors associated with ISR is vital for early detection and appropriate treatment. Hence, this study aimed to evaluate the clinical predictors of ISR specifically in Taiwanese patients. **Methods** We conducted a single-center, retrospective case-control study, enrolling 517 CAD patients undergoing previous coronary stenting and stable angina with positive stress test or acute coronary syndrome (ACS) during follow-up between January 2019 and December 2022 at National Taiwan University Hospital. The patients were categorized into two groups: the ISR group, consisting of individuals who received drug-coated balloon (DCB) treatment (n=177), and the non-ISR group, comprising patients who did not receive DCB treatment (n=340). To gather relevant data, we meticulously reviewed the medical records and analyzed the findings from coronary angiography to assess the clinical characteristics of the patients. **Results** Patients with three-vessel disease (3VD) exhibited a higher prevalence of underlying diseases and were more likely to be taking aspirin and clopidogrel. Moreover, our analysis revealed that age (adjusted odds ratio [aOR] 1.02, 95% confidence interval [CI] 1.00 - 1.04, p = 0.037) and the presence of 3VD (adjusted odds ratio [aOR] 2.15, 95% confidence interval [CI] 1.03 - 4.46, p = 0.039) were significantly associated with an increased risk of coronary ISR. **Conclusions** Older age and 3VD were the independent predictors of coronary ISR in CAD patients receiving coronary stent implantation.

Keywords: coronary artery disease; drug-coated balloon; in-stent restenosis; predictors

1. Introduction

Coronary artery disease (CAD) is one of the major cardiovascular diseases which has been known as the leading cause of death affecting the global human population. Percutaneous coronary intervention (PCI), a procedure aimed at opening blocked arteries and reducing damage to the myocardium, encompasses various techniques such as percutaneous transluminal coronary

angioplasty (PTCA), stent implantation, and the use of drug-coated balloons (DCBs). Back in the early 1970s, stents were not yet available, and PTCA was the sole method used in PCI to address coronary artery stenosis. However, the occurrence of restenosis within six months postoperatively was alarmingly high, reaching approximately 50% [1]. In the 1980s, the introduction of bare-metal stents (BMSs) managed to reduce the six-month restenosis rate to 30% [2]. Over the past decade, the advent of new-generation drug-eluting stents (DESs) incorporating antiproliferative drugs like zotarolimus or everolimus has further decreased the occurrence of in-stent restenosis (ISR) to less than 10% [3]. Additionally, fully bioresorbable vascular scaffolds (BVSs), constructed from naturally occurring and synthetic biodegradable polymers, have emerged as a novel type of stent. These scaffolds provide similar drug delivery capabilities to metallic DESs for a period of six to twelve months after stenting, followed by gradual bioresorption [4]. Through advancements in PCI techniques and the development of innovative stents, the management of CAD has witnessed significant progress, resulting in reduced rates of restenosis and improved patient outcomes.

ISR refers to post-stenting coronary arterial damage followed by neointimal tissue proliferation ≥ 50% of the lumen diameter [5]. The clinical manifestations of ISR can vary widely, ranging from silent ischemia to acute myocardial infarction (AMI). Acute coronary syndrome (ACS), which includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), accounts for more than half of all cases of ISR. Moreover, the presence of ACS in conjunction with ISR independently increases the risk of major adverse cardiac events (MACE) [6]. The significant incidence of severe ISR presentations emphasizes the importance of modifying ISR-related risk factors for secondary prevention.

The mechanisms of ISR arise from vascular injury caused by stent implantation, involving inflammation, proliferation, and matrix remodeling. The inflammatory responses to mechanical stretch, endothelial denudation, and subintimal hemorrhage triggered cascades of proliferative process, including vascular smooth muscle cell (VSMC) proliferation and migration, extracellular matrix synthesis, and resulted in formation of neointimal hyperplasia [7]. In fact, ISR is influenced by multiple factors. Firstly, patient characteristics such as age and comorbid conditions play a role. Secondly, biological factors, including drug resistance, systemic inflammation, neoatherosclerosis, and the presence of calcified nodules, contribute to ISR. Thirdly, genetic factors are associated with the development of neointimal tissue. Fourthly, mechanical factors, such as stent under-expansion, over-dilatation of an undersized stent, and stent fracture, can also contribute to ISR. Lastly, technical factors, including barotrauma outside the stented segment, the presence of residual uncovered atherosclerotic plaques, and stent gaps, may influence the occurrence of ISR [8]. Despite the significant decrease in the incidence of coronary restenosis following stenting, the adoption of stent implantation on a large scale highlights that ISR remains a significant clinical challenge. The average time for ISR to occur is approximately 12 months with DESs and 6 months with BMSs [5,9]. In recent years, several predictors for ISR have been proposed; however, the results have been inconsistent and not yet fully clarified. Consequently, we conducted a single-center, retrospective cohort study to evaluate the clinical predictors of ISR in Taiwanese patients with CAD.

2. Materials and Methods

2.1. Study Design

We conducted a single-center, retrospective case-control study, enrolling 517 CAD patients undergoing previous coronary stenting and stable angina with positive stress test or acute coronary syndrome during follow-up between January 2019 and December 2022 at National Taiwan University Hospital. The patients were divided into two groups: the ISR group, consisting of patients who received drug-coated balloon (DCB) treatment for ISR (n=177), and the non-ISR group, comprising patients who did not receive DCB treatment and did not develop ISR (n=340). The inclusion criteria for the study were as follows: 1) patients above 20 years old, 2) patients who had experienced ISR after coronary stenting with BMSs, DESs, or BVSs and were subsequently treated with DCBs, referred as the ISR group, and 3) patients who had undergone coronary stenting with

BMSs, DESs, or BVSs but did not develop ISR as confirmed by angiographic diagnosis, referred as the non-ISR group. The medical records and coronary angiographic findings of the patients were reviewed to assess their clinical characteristics.

2.2. Patients and Clinical Characteristics

This research involved gathering patients' demographic information, including age, gender, body mass index, and underlying diseases such as hypertension, type II diabetes mellitus, peripheral artery occlusive disease, chronic kidney disease, end-stage renal disease, atrial fibrillation or atrial flutter, heart failure with reduced ejection fraction, and a history of coronary artery bypass graft. Additionally, we analyzed the current cardiovascular medications used by all participants in the study, including antiplatelet drugs, anticoagulants, statins, beta blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and angiotensin receptor-neprilysin inhibitors. The baseline characteristics of these factors were compared to the coronary vessel disease (VD) group, which included one-vessel disease (1VD), two-vessel disease (2VD), and three-vessel disease (3VD). In the population with coronary ISR, we classified the clinical manifestations into silent ischemia, stable angina, and acute coronary syndrome (ACS) for further analysis.

2.3. Coronary Angiographic Analysis

Coronary ISR was defined as the occurrence of post-stenting coronary arterial damage followed by neointimal tissue proliferation that resulted in a reduction of the lumen diameter by at least 50%. The coronary angiographic diagnoses were categorized into different types: one vessel disease (1VD), two vessel disease (2VD), three vessel disease (3VD), and left main (LM) disease. LM disease was defined as ≥ 50% angiographic narrowing of the LM coronary artery, either with or without multi-vessel coronary artery disease (CAD). Furthermore, chronic total occlusion (CTO) was identified as the total occlusion of a coronary artery lasting for at least 3 months based on angiography. CTO represents a particularly complex coronary lesion. The vessels affected by ISR could be the LM coronary artery, left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), ramus intermedius artery (RI), or involve multiple vessels. In our analysis, we examined the number of ISR lesions among patients with ISR and assessed the type of stents used in all study participants.

2.4. Statistical Methods

This research study was divided into three groups: the one vessel disease (1VD), two vessel disease (2VD), and three vessel disease (3VD) groups. A comparison of the VD groups was conducted using the Chi-square test for categorical variables. Baseline characteristics were presented as numbers and percentages (n (%)). Continuous variables were analyzed using one-way analysis of variance (ANOVA), and the results were reported as means and standard deviations (mean ± SD). Logistic regression models were employed in this study to estimate the odds ratio (OR) and 95% confidence interval (CI) to assess the risk associated with all the baseline variables. Potential confounding variables were taken into account, and adjusted odds ratios (aORs) were computed to consider their impact on the relationship between the ISR group and the non-ISR group. A significance level of p ≤ 0.05 was utilized for the statistical tests, and two-tailed p-values were considered significant. All statistical analyses were performed using the SAS System for Windows version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Baseline Characteristics

The results of the study indicated significant differences among the one vessel disease (1VD) group (n=55), two vessel disease (2VD) group (n=144), and three vessel disease (3VD) group (n=318) in terms of age, underlying diseases, and cardiovascular medications. In relation to gender, the

percentage of males in the 1VD group was 70.91%, in the 2VD group was 79.86%, and in the 3VD group was 84.28% (p=0.036). Among the mentioned factors, the 3VD group exhibited the highest proportion of underlying diseases, including hypertension, type II diabetes mellitus, dyslipidemia, chronic kidney disease, end-stage renal disease, and a history of coronary artery bypass graft. Additionally, the use of cardiovascular medications such as aspirin and clopidogrel was more prevalent in the 3VD group (Table 1). Among all the patients with coronary ISR, stable angina (n=125, 71%) accounted for the majority of clinical manifestations, followed by ACS (n=28, 16%), and silent ischemia (n=24, 13%) (Figure 1).

Table 1. Demographic and clinical characteristics.

Variables	1VD (n = 55)	2VD (n = 144)	3VD (n = 318)	P value
Age	66.80 ± 11.28	68.10 ± 11.98	67.77 ± 10.78	0.762
Gender (Male)	39 (70.91)	116 (80.56)	270 (84.91)	0.036
BMI (kg/m2)	25.95 ± 3.79	25.94 ± 3.58	26.23 ± 3.62	0.685
Underlying diseases				
HTN	37 (67.27)	115 (79.86)	268 (84.28)	0.010
T2DM	15 (27.27)	60 (41.67)	179 (56.29)	<0.001
DLP	35 (63.64)	116 (80.56)	229 (72.01)	0.033
PAOD	1 (1.82)	6 (4.17)	15 (4.72)	0.615
CKD	3 (5.45)	10 (6.94)	53 (16.67)	0.003
ESRD	2 (3.64)	5 (3.47)	35 (11.01)	0.010
AF/AFL	10 (18.18)	17 (11.81)	27 (8.49)	0.078
HFrEF	5 (9.09)	22 (15.28)	47 (14.78)	0.499
History of CABG	0 (0)	2 (1.39)	25 (7.86)	0.002
Medications				
Aspirin	27 (49.09)	99 (68.75)	228 (71.70)	0.003
Clopidogrel	21 (38.18)	53 (36.81)	158 (49.69)	0.020
Ticagrelor	1 (1.82)	5 (3.47)	20 (6.29)	0.030
Prasugrel	2 (3.64)	5 (3.47)	13 (4.09)	0.946
NOAC	7 (12.73)	9 (6.25)	19 (5.97)	0.176
Statin	35 (63.64)	102 (70.83)	235 (73.90)	0.276
ACEi /ARB	17 (30.91)	59 (40.97)	133 (41.82)	0.309
Beta blockers	30 (54.55)	75 (52.08)	180 (56.60)	0.661
ARNI	0 (0)	5 (3.47)	13 (4.09)	0.311
Previous stent type				
BMS	6 (10.91)	17 (11.81)	43 (31.52)	0.797
DES	43 (78.18)	120 (83.33)	280 (88.05)	0.099
BVS	6 (10.91)	10 (6.94)	1 (0.31)	-
Primary outcome				
ISR	12 (21.82)	33 (22.92)	132 (41.51)	<0.001

BMI: body mass index, HTN: hypertension, T2DM: type II diabetes mellitus, DLP: dyslipidemia, PAOD: peripheral artery occlusive disease, CKD: chronic kidney disease, ESRD: end stage renal disease, AF: atrial fibrillation, AFL: atrial flutter, HFrEF: heart failure with reduced ejection fraction, CABG: coronary artery bypass

graft, NOAC: non-vitamin K antagonist oral anticoagulant, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, ISR: in-stent restenosis, 1VD: one-vessel disease, 2VD: two-vessel disease, 3VD: three-vessel disease.
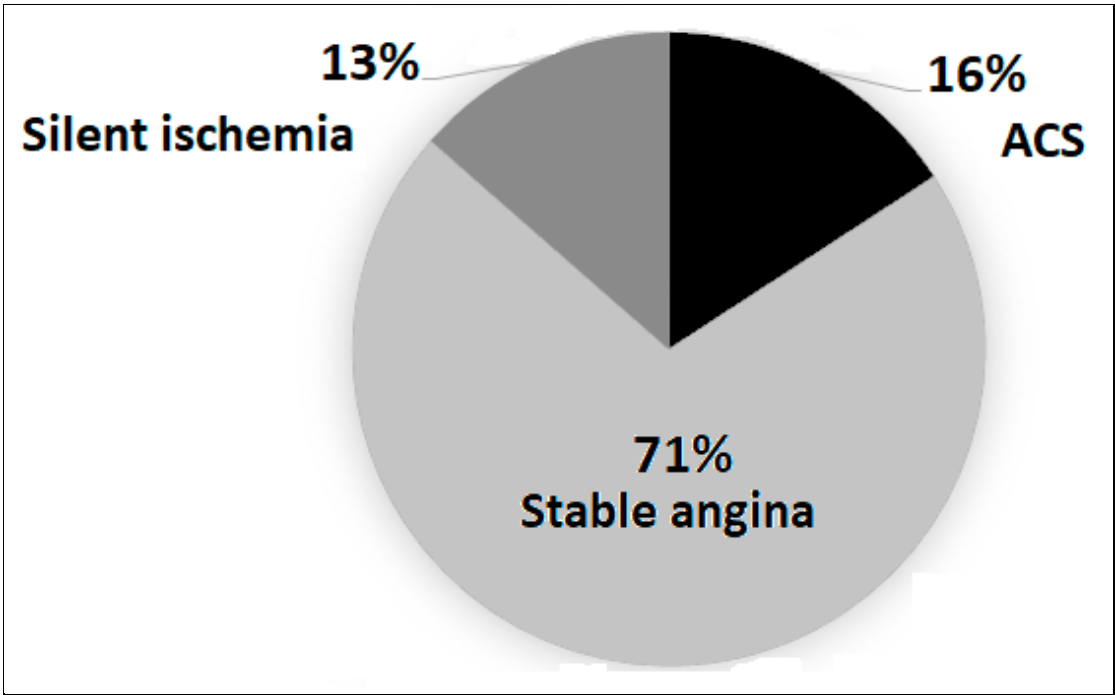

Figure 1. Clinical manifestations of coronary ISR. ACS: acute coronary syndrome.

3.2. Independent Clinical Predictors of Coronary ISR

In Table 2, we performed adjustments for age, BMI, and sex in Model 1. Subsequently, in Model 2, we further adjusted for underlying diseases in addition to age, BMI, and sex. The results of Model 1 showed that patients with three vessel disease (3VD) had a higher risk of coronary ISR compared to the reference group, with an adjusted odds ratio (aOR) of 2.58 (95% confidence interval [CI] 1.30 - 5.13, p = 0.006). Model 2 also demonstrated a significant association between 3VD and increased risk of coronary ISR, with an aOR of 2.34 (95% CI 1.14 - 4.79, p = 0.020), after adjusting for all the specified variables. Furthermore, in Model 3 (Table 3), where adjustments were made for all variables, including age, BMI, sex, and underlying diseases, the analysis revealed that within the age group, there was a significant association between increasing age and the risk of coronary ISR, with an aOR of 1.02 (95% CI 1.00 - 1.04, p = 0.037). Specifically, within the VD group, the 3VD subgroup was found to have a significantly higher risk of coronary ISR, with an aOR of 2.15 (95% CI 1.03 - 4.46, p = 0.039). These findings highlight that both age and the presence of three vessel disease (3VD) are independently associated with an increased risk of coronary ISR.

Table 2. Independent clinical predictors of coronary ISR.

Variables		Model 1	P value	Model 2	P value
		aOR (95% CI)		aOR (95% CI)	
Group of VD	1VD (ref)	1		1	
	2VD	1.05 (0.49 – 2.24)	0.889	1.04 (0.48 – 2.25)	0.917
	3VD	2.58 (1.30 – 5.13)	0.006	2.34 (1.14 – 4.79)	0.020

Model 1: adjusted sex, age, and BMI; Model 2: adjust sex, age, BMI, and underlying diseases.

Table 3. Independent clinical predictors of coronary ISR.

Variables		Model 3	P value
		aOR (95% CI)	
Group of VD	1VD (ref)	1	
	2VD	0.96 (0.44 – 2.10)	0.934
	3VD	2.15 (1.03 – 4.46)	0.039
Age		1.02 (1.00 – 1.04)	0.037
Gender	Female (ref)	1	
	Male	1.00 (0.59 – 1.71)	0.976
BMI (kg/m2)		0.99 (0.94 – 1.05)	0.920
Underlying diseases			
HTN		0.68 (0.40 – 1.17)	0.169
T2DM		1.42 (0.93 – 2.16)	0.100
DLP		0.75 (0.47 – 1.21)	0.254
PAOD		1.42 (0.55 – 3.63)	0.643
CKD		0.91 (0.50 - 1.66)	0.761
ESRD		1.45 (0.68 – 3.08)	0.328
AF/AFL		1.53 (0.67 – 3.47)	0.308
HFrEF		1.28 (0.70 – 2.34)	0.407
History of CABG		1.69 (0.73 – 3.98)	0.218
Medications			
Aspirin		1.39 (0.87 – 2.23)	0.165
Clopidogrel		1.04 (0.67 – 1.62)	0.838
Ticagrelor		0.92 (0.37 – 2.30)	0.867
Prasugrel		0.80 (0.28 – 2.28)	0.681
NOAC		0.74 (0.26 – 2.06)	0.565
Statin		1.29 (0.80 – 2.07)	0.288
ACEi /ARB		1.03 (0.68 – 1.55)	0.887
Beta blockers		1.07 (0.72 – 1.60)	0.707
ARNI		0.69 (0.21 – 2.22)	0.540

Model 3: adjust sex, age, BMI , underlying diseases, and medications.

3.3. Coronary Angiography and Lesion Characteristics

When considering the previous stent type, there was no statistically significant difference observed between the coronary ISR group and the non-ISR group for both BMS and DES (Figure 2). In terms of the coronary lesions, the results of coronary angiography showed significant differences between the ISR group and the non-ISR group. The ISR group had a higher percentage of patients with left main (LM) disease (22% versus 12%, p=0.002), three vessel disease (3VD) (75% versus 55%, p<0.001), and chronic total occlusion (CTO) (44% versus 23%, p<0.001) compared to the non-ISR group (Figure 3). Regarding the location of the coronary ISR, the left anterior descending artery (LAD) accounted for the majority of the affected vessels, with 80 cases (44%). This was followed by the right coronary artery (RCA) with 47 cases (26%), and the left circumflex artery (LCX) with 30 cases (17%) (Figure 4).
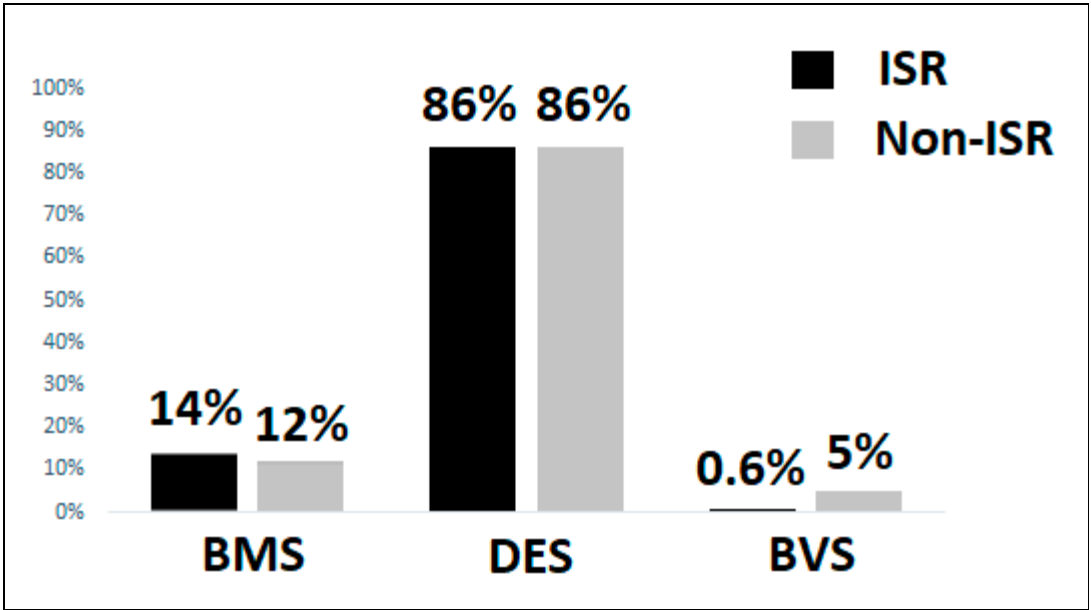
Figure 2. Previous stent types. BMS: bare-metal stent, DES: drug-eluting stent, BVS: bioresorbable vascular scaffold, ISR: in-stent restenosis.
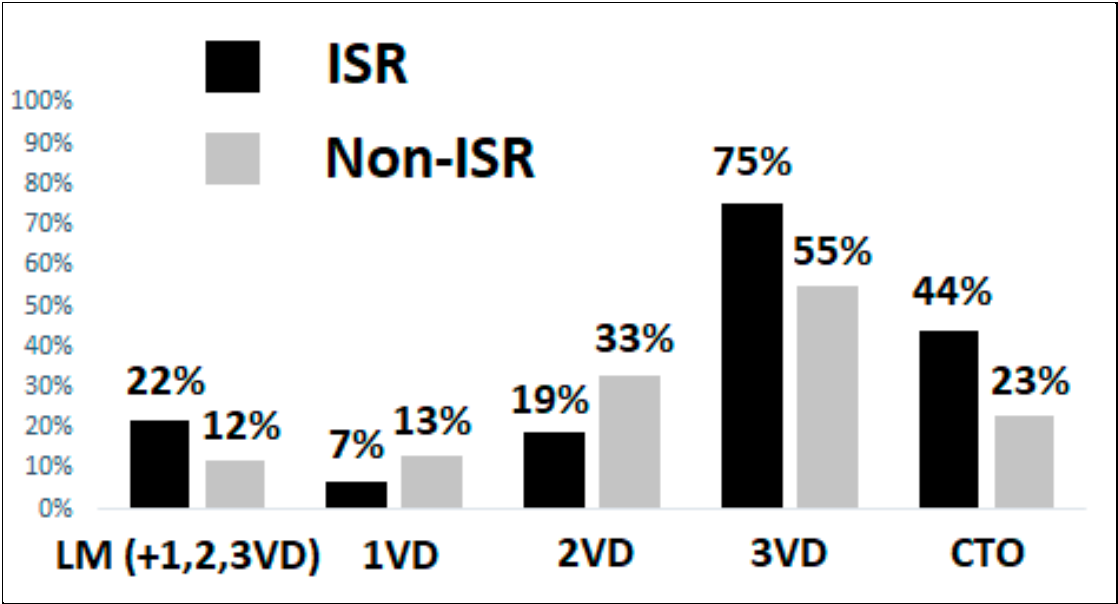

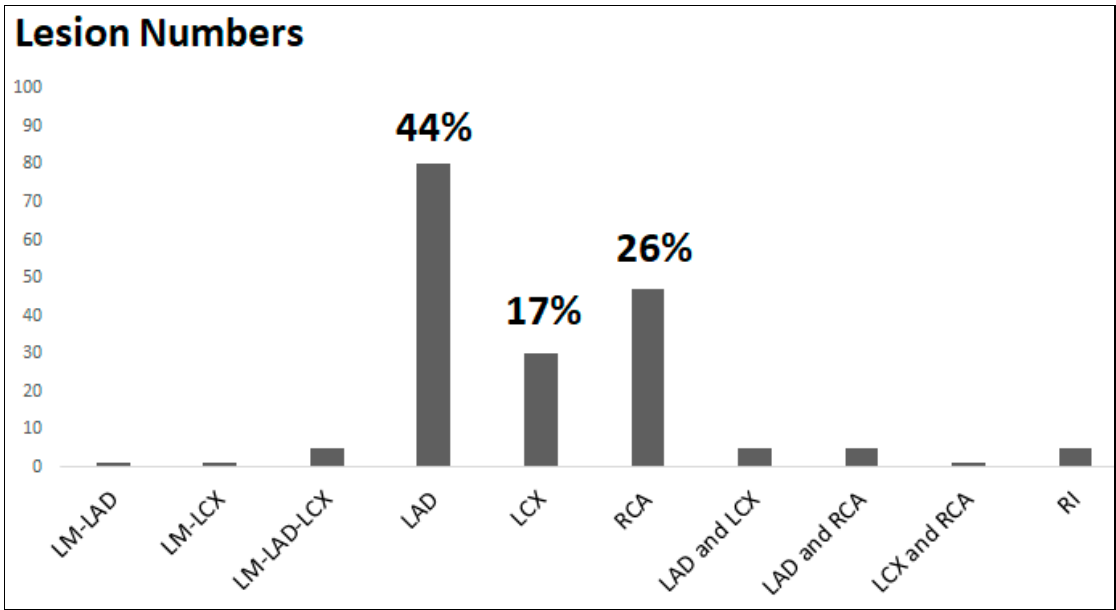**Figure 3. Severity of coronary artery disease.** LM: left main coronary artery, CTO: chronic total occlusion.

Figure 4. Coronary ISR vessel.

4. Discussion

The risk factors associated with coronary ISR have not been completely elucidated. Proposed risk factors for coronary ISR include hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, a history of previous coronary artery bypass graft, and multi-vessel disease [10–14]. Our study revealed that the group with three-vessel disease (3VD) had the highest prevalence of underlying conditions such as hypertension, diabetes, dyslipidemia, chronic kidney disease, end-stage renal disease, and a history of coronary artery bypass graft. These individuals also had a higher usage of cardiovascular medications like aspirin and clopidogrel. However, only older age and the presence of 3VD were identified as independent clinical predictors of coronary ISR. The complexity of CAD with diffuse lesions may contribute to an increased risk of atherosclerosis progression and ISR following coronary stenting [15]. Multi-vessel CAD is often accompanied by various comorbidities and is characterized by smaller vessel size, longer and more diffuse lesions. This poses challenges in selecting an appropriate stent size and length to cover the entire lesion. Consequently, there is a potential for geographical miss during PCI, leading to an increased risk of ISR development [16,17]. Pathological studies have indicated that calcified atherosclerotic lesions can be classified into microcalcification and macrocalcification. Microcalcification is more prevalent in younger patients and is associated with endothelial inflammation and plaque instability, potentially leading to ACS. On the other hand, macrocalcification occurs predominantly in older patients with multi-vessel CAD, making revascularization during PCI more difficult [18,19]. Interestingly, although diabetes has long been considered a major risk factor for coronary ISR [20,21], our study did not demonstrate an increased risk. In the era of DES, the high efficacy of these stents may have mitigated the vulnerability of diabetic patients to stent injury and neointimal proliferation [14].

The incidence of coronary ISR has significantly decreased with the advancements in stent technology and improvements in interventional procedures. New generation DESs have been developed to address the concerns of coronary ISR and enhance the long-term effectiveness of PCI when compared to BMSs [22,23]. Despite these advancements, BMSs continue to be extensively utilized worldwide, with an average adoption rate of approximately 20% [24,25]. When it comes to the likelihood of developing ISR, larger coronary arteries, which are defined as vessels with a lumen diameter greater than 3-3.5 mm, are less prone to this complication than smaller arteries. Consequently, BMSs are often preferred for larger vessels as they provide sufficient space to accommodate neointimal hyperplasia. As a result, the use of BMSs is primarily associated with a higher incidence of aggressive restenosis in cases involving longer lesions or smaller vessels [26–29]. Morice MC et al. also proposed that BMS use might not take higher risk of coronary ISR and need for

repeated revascularization in patients with larger coronary vessels [30]. Similarly, in our study, we observed that coronary ISR did not occur more frequently in patients with BMSs compared to those with DESs. This finding emphasizes that in carefully selected patients with larger coronary vessel diameter, there may not be a necessity to preferentially implant a DES to reduce the risk of future ISR, which substantially decreases the medical costs. Currently, the treatment for CAD is well optimized, including use of dual antiplatelet, renin-angiotensin system blockage and high-strength statins. These treatments may substantially decrease the occurrence of coronary ISR, even in cases involving BMSs.

The clinical presentation of coronary ISR can vary, but it often manifests similarly to CAD, including silent ischemia, angina pectoris, and recurrent cardiac events (unstable angina or ACS). Previous studies have provided insights into the clinical presentations of coronary ISR in patients with BMSs and DESs. It has been found that unstable angina is the most common presentation of BMS ISR, accounting for a range of 26% to 53% of cases, followed by AMI, which occurs in approximately 3.5% to 20% of patients. Similarly, DES ISR is characterized by unstable angina in approximately 16% to 66% of cases and AMI in 1% to 20% of cases [5,31,32]. However, our study yielded unexpected results. We observed that stable angina accompanied by stress-induced myocardial ischemia, as evidenced by myocardial perfusion imaging (MPI), was the predominant clinical presentation of coronary ISR, accounting for 71% of cases. This finding highlights the significance of identifying stress-induced myocardial ischemia through MPI in patients with angina or angina-equivalent symptoms, particularly those at high risk for coronary ISR. It is important to note that the risk of coronary ISR is highest within the first year after stent placement, and gradually decreasing over time. Therefore, regular follow-up tests, including stress tests, electrocardiograms (ECGs), or imaging studies, are recommended for high risk patients to monitor their condition and detect any signs of ischemia. In summary, our study highlight the prevalence of stable angina with stress-induced myocardial ischemia as the main presentation of coronary ISR. Timely identification of ischemia through MPI testing in patients at high risk for ISR may play a crucial role in reducing the incidence of ACS.

In our study, we observed that the left anterior descending (LAD) coronary artery had the highest incidence of ISR among all the study populations, accounting for 44% of all ISR lesions. From an anatomical perspective, the LAD coronary artery differs from the LCX and RCA in several ways. It possesses two sets of branches known as septal branches and diagonal branches. The septal branches perforate the interventricular septum to supply the anterior two-thirds of the septum, while the diagonal branches supply the anterior left ventricle. Coronary ISR can occur in arteries of different sizes, but it is more likely to occur in smaller arteries. Several possible mechanisms may support this hypothesis. Firstly, smaller arteries have a greater density of smooth muscle cells (SMCs) compared to larger arteries. SMCs play a crucial role in the development of coronary ISR as they can proliferate and migrate to the site of injury caused by stent placement. The excessive proliferation of SMCs contributes to the narrowing of the vessel and the development of ISR [33]. Secondly, although DES use can significantly reduce the incidence of ISR, in smaller arteries, there is less surface area available for drug deposition, leading to reduced efficacy in preventing restenosis. Thirdly, smaller arteries are subjected to relatively higher mechanical stresses such as compression, expansion, and flexion while stent placement. These mechanical stresses can cause stent struts to recoil or induce arterial injury, contributing to a higher incidence of ISR [34]. Lastly, smaller coronary arteries poses more challenges to achieve optimal stent expansion and apposition during stent deployment. Inadequate stent expansion or incomplete coverage of the lesion segment may contribute to the development of ISR [8,35].

Limitations

This study had several limitations that need to be acknowledged. Firstly, it was a retrospective study, which means that the results may have been influenced by various confounding factors. Secondly, the study did not compare the treatment modalities of PCI with DCB or new stenting in the population with coronary ISR, which may provide valuable insights into the effectiveness of

different interventions. Thirdly, the analysis of short-term and long-term coronary ISR was hindered by a substantial amount of missing data, potentially limiting the overall conclusions that can be drawn. Lastly, the sample size utilized in the study was relatively small, indicating the need for further validation of the findings in larger populations or among different ethnic groups. By recognizing these limitations, future studies can focus on addressing these issues to enhance the validity and generalizability of the findings.

5. Conclusions

Patients with CAD who are older in age and have three-vessel disease are at a higher risk of developing coronary ISR. Therefore, it is crucial to arrange close follow-up after PCI in these patients. Monitoring and regular check-ups are necessary to detect any potential signs of ISR early and intervene promptly to ensure optimal patient outcomes.

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