JMS 2021;4(1):150-155
UDC:616.132.2-089.844

RISK FACTORS FOR IN- STENT RESTENOSIS IN PATIENTS WITH PERCUTANEOUS CORONARY INTERVENTIONS

Zimbakov Zan [1], Zdravkovski I [1], Parisko E[2], Jovanova S[1]
[1]University Clinic of Cardiology, Clinical Centre "Mother Theresa", Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R of North Macedonia
[2]Clinical hospital " Dr.Trifun Panovski", Bitola R of North Macedonia

Abstract

Percutaneous coronary intervention (PCI) is one of the main treatments for patients with coronary heart disease (CHD), and in-stent restenosis (ISR) after PCI has gradually attracted clinical attention. Although the rates of in-stent restenosis (ISR) have been reduced dramatically with the introduction of drug-eluting stents (DESs), the ISR problem has not been completely resolved.

The aim of our study was to identify the risk factors influencing the likelihood of restenosis after stent implantation.

We retrospectively review 115 patients (mean age 63.4±0.3years) with previous PCI for acute coronary syndrome or stabile angina pectoris, hospitalized at the University clinic of cardiology in Skopje for follow-up coronary angiography.

The data were obtain from coronary intervention database. Seventy two patients were diagnosed as ISR and forty three patients had no significant ISR. Restenosis rates were higher among patients with diabetes mellitus, hiperlipidemia and smoking history and the differences between two groups were statistically significant (all $p<0.05$).

The restenosis rates were higher in patients with BMS compared to first and second generation DESs ($p<0.01$). The smaller (diameter <3mm) and longer stents (>20mm) were associated with more in-stent restenosis with significant statistical difference among group ($p < 0.05$). Predictors of in-stent restenosis were identified with linear regression analyses. The diabetes, hyperlipidemia, stent features were independent risk factors for ISR (all $p < 0.05$).

In conclusion, for patients with PCI risk factors identification and management is warranted to prevent the ISR.

***Keywords*:** percutaneous coronary intervention, in-stent restenosis, risk factor

Introduction

Percutaneous coronary intervention (PCI) is a primary and common treatment for patients with coronary heart disease (CHD).

Although the use of coronary stents brought about a dramatic improvement in patients' clinical and procedural outcomes, the long-term outcome of stent implantation attracted clinical attention by the risk of developing in-stent restenosis (ISR) over time, with significant incidence.

With bare-metal stents (BMS), the incidence of ISR was as high as 20–40%, and with drug-eluting stent (DES), the incidence still remained about 10% [1].

It is generally believed that ISR is one of the most important prognostic factors after PCI. Presently, the mechanism of ISR has not been fully elucidated and the factors affecting ISR after PCI have not been clearly defined. As it is known ISR is due to the formation of intimal hyperplasia mediated by biological, genetic, mechanical, technical and complex factors related to the patient. This morphologic change and subsequent vessel narrowing increase heart disease events rate.

Therefore, early recognition and prevention of ISR is particularly important. The clinical observations suggest that patients with multiple risk factors continue to show increased rates of restenosis with late lumen loss and many studies have discussed the factors influencing ISR.

Despite the influence of the interventional procedure per se, lesion characteristics and stent features, the risk for in-stent restenosis includes the patient's clinical characteristics, the vascular mechanical factors, the histology factors, the molecular-level mechanism and genetic factors [2,3,4].

So, determining the risk factors of ISR after PCI will help in identifying patients with a risk of restenosis and can focus the optimal PCI strategy to be plan and undertaken and guided general measurements and intervention on major risk factors connected with ISR.

The aim of this study was to explore some of the risk factors associated with in-stent restenosis that can help in selection of patients at the highest risk for restenosis.

Patients and Methods

We review 115 patients with previous PCI for acute coronary syndrome or stabile angina pectoris, hospitalized at the University clinic of cardiology in Skopje for follow-up coronary angiography. The mean age of the patients was 63.4±0.3 years and there were 92 males (80%) and 23 females (20%).

Statistical analysis

Coronary angiography was performed according the standard protocol and ISR was defined as a reduction in lumen diameter by over 50% after PCI.

Based on coronary angiography, the cases were divided into ISR and non-ISR group. The ISR group consisted of 72 cases and the non-ISR group consisted of 43 cases.

Medical history with baseline characteristics (age, gender, history of diabetes, hypertension, smoking history, hyperlipidemia, BMI), features of coronary stents and stent status (type: BMS or DES, position, stent length and stent diameter) were analyzed retrospectively.

This study was approved by the Medical Ethics Committee of Medical faculty in Skopje and all the included patients had signed written informed consent.

Data are expressed as mean±SD for continuous variables, and data for the categorical variables are expressed as the number and the percentage of patients.

The results between the two groups were compared via an unpaired Student's *t* test, and Chi-square test. A linear regression analysis was applied to verify the independent predictors for ISR. A p-value of less than 0.05 was considered statistically significant. SPSS software was used for analyses.

Results

Table 1 compares the baseline characteristics of patients with ISR (n-73) with those without significant ISR (n-42). There was no significant difference for age (p=0.727) and gender (p=0.986) among groups. There were no significant differences on the hypertension, diabetes and smoking history

Restenosis rates were lower in patients with hypertension but statistically insignificant compared with non-ISR group (74% vs.77%, p=0.232). There was significant difference among ISR and non-ISR group for diabetes mellitus and hyperlipidemia (42% vs. 36% and 32% vs 24%, respectively, p<0.05). There was no difference for BMI among both groups. Current smokers had higher restenosis rates (29% vs. 22%, p<0.01).

Table 1. Comparison of baseline characteristics between ISR and non-ISR cases

Variable	ISR (n=72)	non-ISR (n=43)	p-value
Age (years)	63.2±9.8	63.9±14.6	0.727
Male n (%)	58(80%)	35(81%)	
Female n (%)	14(20%)	8(19%)	
BMI	28.5±2.9	28.4±3.4	0.838
Smoking, n (%)			
current smoker	21(29%))	10(22%)	<0.05
ex-smoker	11(15%))	7(16%))	
Hypertension, n (%)	53(74%)	3(77%)	0.232
Diabetes mellitus, n (%)	30(42%)	16(36%)	<0.05
Hyperlipidemia	23(32%)	10(24%)	<0.05

Procedural characteristics are given in table 2. With respect to stent type at the index procedure, the restenosis rates were higher in patients with BMS compared to first and second generation DESs (31% vs. 7% for BMS, 32% vs. 44% for first generation DESs and 37% vs. 49% for second generation DESs, p<0.01).

There was difference in the stent position (index coronary artery) between ISR and non- ISR group of patients. More patients with stent position in circumflex artery demonstrated in-stent restenosis.

There were statistical differences for stent features (stent diameter and stent length) between ISR and non-ISR group. The smaller (diameter <3mm) and longer stents (>20mm) were associated with more in-stent restenosis with significant statistical difference among group (27% vs. 15%; 36% vs. 26%, respectively, all $p < 0.05$).

Table 2. Comparison of stent features between ISR and non-ISR cases

Variable	ISR (n=72)	non-ISR (n=43)	p-value
Stent type			
BMS	22(31%)	3(7%)	<0.001
DES-first gener.	23(32%))	19 (44%)	<0.001
DES -second gener.	27(37%)	21(49%)	<0.01
Stent' length			
≤ 20mm	46(64%)	32(74%)	<0.05
>20mm	26(36%)	11(26%)	
Stent' diameter	3.11±0.49	3.25±0.41	<0.05
≥3mm	52(73%)	36(85%)	<0.005
<3mm	20(27%)	7(15%)	<0.005
Stent position			
LMN	3(4%)	1(2%)	
LAD/diag.	29(40%)	22(51%)	<0.05
RCA/PDA	30(42%)	17(40%)	
Cx/OM	10(14%)	3(7%)	<0.01

Table 3 indicated the assignment of Cox logistic regression analysis. As it is shown diabetes (HR 2.8, CI 1.3-4.1), hyperlipidemia (HR 1.21 CI 0.7-1.6), smoking history (HR 1.23, CI 0.8-2.7), bare-metal stent (HR 4.07, CI 2.2-7.3), stent diameter < 3 mm (HR 2.5, CI 0.97-4.0), stent length > 20 mm (HR 1.9, CI 1.3-3.1) were independent risk factor for ISR (all $p < 0.05$).

Table 3. Cox regression analysis of risk factors and stent features for occurrence of ISR

Variables	HR	95% CI	p-value
Clinical characteristic			
Hypertension	0.81	0.3-2.1	0.84
Smoking	1.23	0.8-2.7	0.042
Hyperlipidemia	1.21	0.7-1.6	0.037
Diabetes mellitus	2. 8	1.3-4.1	0.025
Stent features			
BMS	4.07	2.2-7.3	0.014
Stent length >20mm	1.9	1.3-3.1	0.032
Stent diameter<3mm	2.5	0.97-4.0	0.028

HR: hazard ratio, CI: confidence intervals.

Discussions

PCI is currently the main effective treatment option for CHD. Despite the effectiveness and clinical significance of PCI, in-stent restenosis (ISR) is a difficult problem in the treatment of CHD by PCI, and it is also a hotspot and difficult point of current research.

Although drug-eluting stents (DES) have significantly reduced the incidence and prevalence of coronary in-stent restenosis (ISR), ISR still occurs in approximately 10% of patients in real-world practice.

At present, the pathogenesis of ISR after PCI is not fully understood. Many reports have proposed vascular intimal hyperplasia due to intimal proliferation and infiltration of local inflammatory cells as the potential pathogenetic mechanism in ISR.

The researchers suggest that the intimal hyperplasia is mediated by biological, genetic, mechanical, technical and complex factors related to the patient. As many clinical observations suggest strong association of this pathomorphologic change and subsequent vessel narrowing with increase heart disease events rate, early recognition and prevention of ISR with identification of patients at the highest risk for restenosis is particularly important. This would help the optimal PCI strategy to be plan and undertaken and guided general measurements and intervention on major risk factors connected with ISR [3,4].

Although most of the studies on prediction of restenosis antedate the use of stents, there has been no change in the clinical variables predicting restenosis. Diabetes mellitus continues to be a strong clinical predictor of restenosis. The patient's poor blood glucose control aggravate the process of protein glycosylation and oxidation, damaging the vascular endothelium and initiate atherosclerotic plaque, which is related to ISR. High blood pressure accelerates the shear force on the arterial wall, damages the vascular endothelial cells, and increases the incidence of ISR. So, for patients with a history of diabetes or hypertension, strictly controlling blood pressure and sugar is beneficial to reduce the risk of ISR.

High levels of LDL-C stimulate inflammation, damage vascular endothelial cells, and promote the deposition of cholesterol in the blood vessel wall. It's been reported that controlling cholesterol intake can reduce the incidence of CHD. Therefore, standardizing medication after PCI is very important [3,4].

There are many studies undertaken to identify the risk factors for ISR in patients with PCI. In the study of Kastrati et al. analysis of 1349 patients revealed the strongest multivariate predictors for in-stent restenosis to be diabetes mellitus, placement of multiple stents, and post-stent MLD - 3mm. This study was performed in the initial stent era; it had incomplete angiographic follow-up and used different post-stent antithrombotic regimens [5].

Chang at co-workers retrospectively reviewed the clinical data, laboratory indicators, and stent features of 1132 patients after PCI. The incidence of restenosis was 8.21%, consistent with related report in which the incidence of ISR was reported to be around 10%.The results of study have found that the hypertension, diabetes, history of smoking, left anterior descending artery, diameter of

stent <3 mm, the length of stent > 20 mm were independent risk factors for ISR in patients with PCI [6].

Mercado and coll. analyzed 9120 treated lesions in 8156 patients chosen from a pooled 19 different studies and found poor ability for clinical variables to discriminate between patients who did and did not develop restenosis [7].

The study of Singh and coll. is the largest in the current era with restenosis as one of the major end points. The aim of the study was to predict restenosis solely on the basis of pre-procedural clinical and angiographic variables.

The authors have been reported that in group of pts with almost no risk factors for restenosis, the restenosis rates were 28% and conversely, patients with multiple adverse clinical and angiographic variables placed the patient at a very high risk of restenosis. This finding can be helpful in risk stratifying very-high-risk patients for subsequent restenosis [8].

Patients with treated diabetes mellitus had a 45% higher risk of restenosis compared with non-diabetics. They also documented the correlation of small vessel size, complex type C lesions, longer length of the lesion, ostial location, and previous angioplasty with risk of restenosis [8].

Cho and coll reported that age, diabetes, the use of first generation DES, were significant predictors of ISR with ACS presentation and the use of aspirin, clopidogrel, RAS blocker, and the use of second generation DESs prevented ISR with ACS presentation [10].

Many studies have reported that the incidence of ISR of anterior descending branch is significantly higher than that of left circumflex branch and the right coronary artery [5,6,7], but in our study there we more restenosis in patients with PCI in circumflex artery.

Some authors have pointed out that both the diameter of the blood vessel and the length of the stent have a certain correlation with the ISR and suggest that optimal plan for PCI, especially for small vessel disease or diffuse disease is necessary to reduce the incidence of ISR [7,8,9].

Our study has found that stent diameter < 3 mm and stent length > 20 mm are risk factors for ISR, suggesting the importance of optimizing PCI strategy in patients with CHD.

Limitation of the study

There are several limitations to this study. First, this is a retrospective analysis and is therefore might be some bias and heterogeneity in the study groups. Second, this had a small sample size, a nonrandomized design, and a lack of strict entry criteria so it might be not power enough to detect the potential related risk factors and more studies on the risk factors for the ISR are needed in the future.

Additional study and analysis are needed to detect the influence of medical therapy (antiplatelet treatment, use of ACE inhibitors, beta blockers, Ca^{++} channel blockers etc and angiographic features of the lesions and coronary status in general.

Conclusion

This study demonstrates that for patients with PCI, diabetes, smoking history, hypelipidemia, stent features as BMS, stent diameter <3 mm, stent length > 20 mm are independent risk factors for ISR and interventions and measures targeted on those risk factors are warranted to prevent the ISR.

Reference

1. Her AJ and Shin ES. Current Management of In-Stent Restenosis . Korean Circ J. 2018 May;48(5):337-349, https://doi.org/10.4070/kcj.2018.0103
2. Kokkinidis DG, Waldo SW, Armstrong EJ. Treatment of coronary artery in-stent restenosis. Expert Rev Cardiovasc Ther 2017;15(3):191-202. Doi: 10.1080/14779072.2017.1284588. Epub 2017 Jan 31.
3. Alraies MC, Darmoch F, Tummala, R, Waksman R. Diagnosis and management challenges of in-stent restenosis in coronary arteries
4. Kibos A, Campeanu A, Tintoiu I. Pathophysiology of coronary artery in-stent restenosis. Acute Card Care. 2007;9(2):111-9. doi: 10.1080/1748294070126328
5. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol*. 1997;30:1428–1436.

6. Cheng G, Chang FJ, Wang Y, You PH et al. Factors influencing stent restenosis after perculatenous coronary intervention in patients with coronary heart disease: A clinical trial based on 1-Year Follow-Up. Med Sci Monit. 2019 Jan 8;25:240-247.doi: 10.12659/MSM.908692.
7. Mercado N, Boersma E, Wijns W, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol*. 2001;38:645–652.
8. Singh M, Gersh B, McClelland R, at al. Clinical and Angiographic Predictors of Restenosis After Percutaneous Coronary Intervention Insights From the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) Trial . *Circulation*. 2004;109:2727-2731.)
9. Magalhaes MA, Minha S, Chen F, Torguson R, Omar AF, Loh JP, et al. Clinical presentation and outcomes of coronary in-stent restenosis across 3-stent generations. Circ Cardiovasc Interv 2014;7:768-76.
10. Jae Young Cho. Identification of Risk Factors Influencing In-Stent Restenosis with Acute Coronary Syndrome Presentation. Chonnam Med J 2017;53:203-210