

Factors Associated with In-stent Restenosis in Patients Following Percutaneous Coronary Intervention

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ABSTRAK

Tujuan: mengetahui faktor-faktor yang berhubungan dengan In-Stent Restenosis (ISR) pada pasien pasca Percutaneous Coronary Intervention (PCI). **Metode:** desain penelitian ini ialah potong lintang retrospektif dengan menggunakan rekam medik pasien pasca PCI yang menjalani follow-up angiografi antara bulan Januari tahun 2009 hingga Maret 2014 di Pelayanan Jantung Terpadu/ RSUPN dr. Cipto Mangunkusumo. In-Stent Restenosis dinyatakan apabila diameter stenosis pada saat follow-up angiografi sebesar ≥ 50 persen, baik di dalam stent maupun menjulur sejauh lima mm keluar dari ujung proksimal atau distal stent. **Hasil:** didapat 289 subyek penelitian yang terdiri atas 133 subyek dengan ISR dan 156 tanpa ISR. Kejadian ISR pasca PCI pada penggunaan Bare-Metal Stent (BMS) dan Drug-Eluting Stent (DES) yaitu berturut-turut sebesar 61,3% dan 40,7%. Tipe stent (OR=4,83; 95% IK 2,51-9,30), panjang stent (OR=3,71; 95% IK 1,99-6,90), lesi di bifurkasi (OR=2,43; 95% IK 1,16-5,10), merokok (OR=2,30; 95% IK 1,33-3,99), diameter pembuluh darah (OR=2,18; 95% IK 1,2-3,73), hipertensi (OR=2,16; 95% IK 1,16-4,04) dan diabetes mellitus (OR=2,14; 95% IK 1,23-3,70) merupakan faktor prediksi terjadinya ISR. **Kesimpulan:** tipe stent, panjang stent, lesi di bifurkasi, merokok, diameter pembuluh darah, hipertensi dan DM merupakan faktor-faktor yang berhubungan dengan ISR pada pasien pasca PCI.

Kata kunci: bare-metal stent; drug-eluting stent; in-stent restenosis.

ABSTRACT

Aim: to determine factors associated with In-Stent Restenosis (ISR) in patients following Percutaneous Coronary Intervention (PCI). **Methods:** a retrospective cross-sectional study was conducted using secondary information from medical records of post-PCI patients who underwent follow-up of angiography PCI between January 2009 and March 2014 at The Integrated Cardiovascular Service Unit, Cipto Mangunkusumo Hospital, Jakarta. Angiographic ISR was defined when the diameter of stenosis $\geq 50\%$ at follow-up angiography including the diameter inside the stent and diameter with five-mm protrusion out of the proximal and distal ends of the stent. **Results:** there were 289 subjects including 133 subjects with and 156 subjects without ISR. The incidence of ISR in patients using of bare-metal stent (BMS) and drug-eluting stent (DES) were 61.3% and 40.7%, respectively. Factors associated with ISR are stent-type (OR=4.83, 95% CI 2.51-9.30), stent length (OR=3.71, 95% CI 1.99-6.90), bifurcation lesions (OR=2.43, 95% CI 1.16-5.10), smoking (OR=2.30, 95% CI 1.33-3.99), vascular diameter (OR=2.18, 95% CI 1.2-3.73), hypertension (OR=2.16, 95% CI 1.16-4.04) and diabetes mellitus (OR=2.14, 95% CI 1.23-3.70). **Conclusion:** stent type, stent length, bifurcation lesions, smoking, vascular diameter, hypertension and DM are factors associated with ISR in patients following PCI.

Key words: bare-metal stent; drug-eluting stent; in-stent restenosis.

INTRODUCTION

Advanced science and knowledge has allowed us to perform Percutaneous Coronary Intervention (PCI) for complex lesions of coronary arterial disease (such as multiple vessel and left main disease), which is characterized by the increasing number of PCI procedures.^{1,2} A statistical report in 2014 about heart disease and stroke in the United States demonstrated that there is an increasing number of PCI procedures in both men and women.³ Moreover, data between 2002 and 2005 reported that there is also a greater number of coronary revascularization using PCI procedures compared to Coronary Arterial Bypass Graft.⁴

The increasing number of PCI procedures worldwide indicates that there is an increasing use of intracoronary stent covering as many as 75 to 80 percent.⁵ However, the procedure of stent deploy during PCI will stimulate the growth of Smooth Muscle Cells (SMC).⁶ The smooth muscle cells will then migrate from the tunica media to intima. The cells subsequently will proliferate and develop the Neo Intimal Hyperplasia (NIH), which has important role in the development of stenotic lesion.⁷ The excessive NIH growth will lead to In-Stent Restenosis (ISR).^{6,8}

The intention of using Drug-Eluting Stent (DES) in PCI procedure is to reduce the incidence of ISR caused by the use of Bare-Metal Stent (BMS) and it is demonstrated by the increasing number of DES utilization compared to the BMS.^{3,9} However, the incidence of ISR in patients following PCI, either using DES or BMS remains high.¹⁰⁻¹² Therefore, our study was aimed to identify factors associated with ISR.

METHODS

The design of our study was retrospective cross-sectional using secondary data from medical records of post PCI patients who underwent follow-up angiography of PCI in the period between January 2009 and March 2014 at The Integrated Cardiovascular Service Unit/ National Central General Hospital of dr. Cipto Mangunkusumo, Jakarta. Extraction of secondary data was performed between November and March 2014. The inclusion criteria were post

PCI patients who had undergone follow-up angiography within ≥ 6 months. The exclusion criteria were post-PCI patients without medical record data or angiographic documentation.

The dependent variable in our study was ISR measured based on the Quantitative Coronary Angiography (QCA) evaluation. ISR was defined when the diameter of stenosis $\geq 50\%$ at follow-up angiography including the diameter inside the stent and diameter with five-mm protrusion out of the proximal and distal ends of the stent. The independent variables in our study were: (1) clinical variables such as age, sex, diabetes mellitus (DM), hypertension, chronic kidney disease (CKD) and smoking; (2) variables on lesions including the vascular diameter, the Left Anterior Descending (LAD) lesion, ostial lesion, chronic total occlusions (CTO) lesion, bifurcation lesion, and (3) variables on the procedure, i.e. the type of stent, the length of stent and maximal balloon pressure. Sample size was calculated based on formula of sample size for hypothetical study with different proportion and two independent populations.

Data analysis was performed using SPSS statistical analysis computer software. To analyze the correlation between independent and dependent variables, which both are categorical data, the chi-square statistical test was performed. The independent variables, which by bivariat analysis had p value < 0.25 were included in multivariate analysis. To identify factors of independent variables associated with ISR, a multivariate analysis was performed using double logistic regression test. To identify independent variables that had some effect on dependent variables, the effect was evaluated and expressed as Odd Ratio (OR). Our study had been approved by the Ethical Committee, Faculty of Medicine, University of Indonesia.

RESULTS

There were 289 subjects including 133 subjects with (46%) and 156 subjects without (54%) ISR (**Table 1**). The incidence of ISR in the use of Bare-Metal Stent (BMS) and Drug-Eluting Stent (DES) were respectively 61.3% and 40.7%.

Based on bivariate analysis, we found nine independent variables with $p < 0.25$ including age,

Table 1. Basic characteristics of the subjects (n=289)

Characteristics	n (%)
Age (years), median (IQR)	61 (54; 67)
Age ≥60, n (%)	147 (50.9)
Sex Male, n (%)	224 (77.5)
Clinical diagnosis during ISR, n (%)	
- APS	256 (88.6)
- UAP	23 (8.0)
- NSTEMI	6 (2.1)
- STEAMI	4 (1.4)
Time frame for follow-up angiography (months), median (IQR)	15 (11; 21)
- 6 to 12	114 (39.6)
- >12 to 24	120 (41.7)
- >24	54 (18.8)
Smoking, n (%)	166 (57.4)
Diabetes Mellitus, n (%)	110 (38.1)
Hypertension, n (%)	215 (74.4)
CKD, n (%)	93 (32.2)
Site of lesion, n (%)	
- RCA	83 (28.7)
- LCX	50 (17.3)
- LAD	150 (51.9)
- LM	6 (2.1)
Ostial lesion, n (%)	25 (8.7)
CTO lesion, n (%)	18 (6.2)
Bifurcation lesion, n (%)	45 (15.6)
Stent type, n (%)	
- BMS	75 (26.0)
- DES	214 (74.0)
Stent length (mm), median (IQR)	28 (18; 40.50)
Stent length, n (%)	
- >40	72 (24.9)
- ≤40	217 (75.1)
Maximal balloon pressure (atm), median (IQR)	16 (12; 16)
Maximal balloon pressure, n (%)	
- <14	80 (27.7)
- ≥14	209 (72.3)
Vascular diameter (mm), median (IQR)	2.99 (2.68; 3.49)
Vascular diameter, n (%)	
- <3	147 (50.9)
- ≥3	142 (49.1)

Note: Median (percentile 25; percentile 75) for data without normal distribution

smoking, DM, hypertension, CKD, bifurcation lesion, type of stent, length of stent and vascular diameter. The independent variables with results of bivariate analysis of $p < 0.25$ were included in the multivariate analysis (**Table 2**). The results of multivariate analysis using double logistic regression test demonstrated that there were seven independent variables that had significant correlation with ISR (**Table 3**).

DISCUSSION

There was a greater number of male than female subjects. It is consistent with statistical report on heart disease and stroke in the United States in 2014, which demonstrated that there are more male subjects compared to female subjects.³

The time frame for follow-up angiography following the PCI in our study, either using BMS or DES was 15 months, which was longer compared to other studies.¹³ However, Sukhija et al¹⁴ also had long time frame for follow-up angiography in post-PCI patients with DM, i.e. 16 months (± 2 months).¹⁴

Statistical report in 2014 found that there is higher utilization of DES for PCI procedures compared to the BMS.³ Our study also found that the use of DES in PCI procedure was more common than BMS.

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Results of studies conducted by Mohan and Dall¹⁵ as well as Bo et al¹⁶ showed that each study found lower incidence of ISR following PCI procedure when using DES compared to using BMS (7.7% vs. 33% and 23.2% vs. 48.8%, respectively). Moreover, in post-PCI patients who also had DM, Sukhija et al¹⁴ found a high incidence of ISR (62%). Results of other studies also demonstrated the lower incidence of ISR in post-PCI patients when using DES compared to BMS.¹⁰⁻¹² In our study, the incidence of ISR in post-PCI patients using DES was also found lower than those using BMS (40.7% vs. 61.3%) (**Table 2**).

Table 2. Factors associated with in-stent restenosis

Variables	With ISR (n=133)	Without ISR (n=156)	P value	OR (95% CI)
Age ≥60, n (%)	59 (40.1)	88 (59.9)	0.054	0.62 (0.39 – 0.98)
Sex Female, n (%)	27 (41.5)	38 (58.5)	0.495	0.79 (0.45 – 1.38)
Smoking, n (%)	88 (53.0)	78 (47)	0.008	1.96 (1.21 – 3.15)
Diabetes mellitus, n (%)	59 (53.6)	51 (46.4)	0.056	1.16 (1.01 – 2.65)
Hypertension, n (%)	106 (49.3)	109 (50.7)	0.076	1.69 (0.98 – 2.91)
CKD, n (%)	36 (38.7)	57 (61.3)	0.112	0.65 (0.39 – 1.07)
LAD lesion, n (%)	65 (43.3)	85 (56.7)	0.404	0.80 (0.50 – 1.27)
Ostial lesion, n (%)	14 (56.0)	11 (44.0)	0.402	1.55 (0.68 – 3.54)
CTO lesion, n (%)	8 (44.4)	10 (55.6)	1.000	0.93 (0.36 – 2.44)
Bifurcation lesion, n (%)	28 (62.2)	17 (37.8)	0.027	2.18 (1.13 – 4.19)
Stent type, n (%)				
- BMS	46 (61.3)	29 (38.7)	0.003	2.32 (1.35 – 3.97)
- DES	87 (40.7)	127 (59.3)		
Stent length (mm), n (%)				
- >40	46 (63.9)	26 (36.1)	0.001	2.64 (1.52 – 4.59)
- ≤40	87 (40.1)	130 (59.9)		
Balloon pressure (atm), n (%)				
- <14	40 (50.0)	40 (50.0)	0.479	1.25 (0.74 – 2.09)
- ≥14	93 (44.5)	116 (55.5)		
Vascular diameter (mm), n (%)				
- < 3	78 (53.1)	69 (46.9)	0.020	1.79 (1.12 – 2.86)
- ≥ 3	55 (38.7)	87 (61.3)		

One of possible reasons for the high ISR incidence in our study is increased inflammatory response, which is consistent with the results of a study conducted by Alwi¹⁷ who found high inflammatory response in patients with Acute Coronary Syndrome/ACS (DM with ACS, DM with Coronary Heart Disease/CHD, non-DM ACS and non-DM CHD) in Indonesian population.

Table 3. Multivariate analysis on factors associated with in-stent restenosis

Variables	p	OR (95% CI)
Stent type	0.001	4.83 (2.51 – 9.30)
Stent length	0.001	3.71 (1.99 – 6.90)
Bifurcation lesion	0.019	2.43 (1.16 – 5.10)
Smoking	0.003	2.30 (1.33 – 3.99)
Vascular diameter	0.005	2.18 (1.27 – 3.73)
Hypertension	0.016	2.16 (1.16 – 4.04)
DM	0.007	2.14 (1.23 – 3.70)

The Drug-Eluting Stent has grooves or ridges coated with polymers containing antiproliferation drugs against SMC on vascular wall; therefore, the post-PCI NIH development can be reduced.¹⁸ Mose et al¹⁹ and Degertekin et al²⁰ found low volume of NIH in post-PCI patients who used DES compared to those using BMS. In patients with STEAMI who underwent PCI, Giglioli et al²¹ also found low ISR incidence in DES users compared to those who used BMS. Cassese et al²² and Solinas et al²³ also found low ISR incidence in post-PCI patients using DES. Furthermore, in DM patients who underwent PCI, Sukhija et al¹⁴ and Boyden et al²⁴ demonstrated low ISR incidence when using DES. Likewise, our study also found that DES utilization in post-PCI patients is a protective factor against the development of ISR.

In post-PCI patients with DES, Hong et al²⁵ found that stent length (>40 mm) as a predictor of ISR development. Cassese et al also found

that each 10-mm increase of stent length is a predictor of ISR development.²² Furthermore, Kang et al⁸ and Kastrati et al¹³ found that stent length is a predictor of ISR development in post-PCI patients with DES. Our study also found that stent length (>40 mm) is a predictor for developing ISR.

In post-PCI patients with BMS, Park and Park²⁶ found bifurcation lesion as another predictor for developing ISR; while in post-PCI patients with BMS who had small vascular diameter, Lijima et al²⁷ also found that bifurcation lesion is a predictor of ISR development. Likewise, our study also found bifurcation lesion as a predictor for developing ISR.

In DM patients who underwent PCI using DES, Hong et al²⁸ found smoking as a predictor of ISR development. Moreover, in post-PCI patients with BMS, Park and Park²⁶ also found smoking as a predictor for developing ISR. Our study also found that smoking is a predictor for ISR development.

The diameter of coronary blood vessel is associated with the incidence of ISR.²⁹ Although there was no difference regarding maximal balloon pressures during PCI procedure with BMS between the group with small and large diameter, but Akiyama et al³⁰ found increased incidence of ISR in the group with small diameter. Similar results are also found by Kastrati et al¹³ and Cassese et al²² who found reduced vascular diameter of each 0.5 mm is a predictor for ISR development. Our study also found that the size of vascular diameter is a predictor for developing ISR.

Back et al found that hypertension is an important factor for developing restenosis in patients following percutaneous transluminal coronary angioplasty.³¹ Moreover, Mohan and Dhall¹⁵ found a significant correlation between hypertension and ISR. Our study also found that hypertension is a predictive factor for developing ISR.

The results of serial IVUS study by Kornowski et al³² found that the number of narrowed minimal lumen diameter and NIH growth in post-PCI patients who also suffered from DM is higher than those without DM.

A multi-analysis study about the correlation between DM and ISR conducted by Qing et al³³ found that DM is a predictor for developing ISR. The results of IVUS study in post-PCI patients using DES conducted by Rothera et al³⁴ also found DM as a predictor of ISR development. Based on results of multivariate analysis in post-PCI patients with BMS, Park and Park²⁶ found that DM is a predictive factor for developing ISR. By conducting a multi-analysis study, Cassese et al²² found DM as a predictor of ISR development, either using BMS, first or second generation DES. Likewise, our study also found that DM is a predictor of ISR development.

Our study has some limitations such as (1) it was an analytical retrospective and single-centered study; (2) it did not evaluate other factors associated with ISR for example the type of DES, morphology on type of lesions (according to the classification of American Heart Association/AHA), platelet resistance test or evaluation on inflammatory response (including igh-sensitivity C Reactive Protein/Hs-CRP). Further studies are necessary by implementing (1) prospective cohort and multi-centered method and (2) further evaluation on other factors associated with ISR such as the type of DES, morphology on type of lesion (AHA), platelet resistance test and evaluation on inflammatory response (Hs-CRP).

CONCLUSION

Stent type, stent length, bifurcation lesions, smoking, vascular diameter, hypertension and DM are factors associated with ISR in patients following PCI.

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