Factors Influencing Stent Restenosis After Percutaneous Coronary Intervention in Patients with Coronary Heart Disease: A Clinical Trial Based on 1-Year Follow-Up

Background: This study observed the incidence of in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) and discusses the risk factors of ISR based on clinical data, coronary angiography, and stent features, to provide a theoretical basis for the prevention and treatment of ISR.

Material/Methods: We selected 1132 cases who received stent implantation at the Shaanxi People’s Hospital from June 2014 to June 2016 and were followed up by coronary angiography within 1 year. Based on coronary angiography, the cases were divided into ISR and non-ISR groups. ISR was defined as a reduction in lumen diameter by over 50% after PCI. The ISR group consisted of 93 cases and the non-ISR group consisted of 1039 cases. Medical history, biochemical indicators, features of coronary artery lesions, and stent status were analyzed retrospectively. Risk factors of ISR were identified by univariate and multivariate logistic regression analyses.

Results: Among 1132 cases, 93 cases had ISR, with the overall incidence of 8.21%. Univariate and multivariate logistic regression analyses indicated that postoperative hypersensitive C-reactive protein (hs-CRP) levels (OR=2.309, 1.579–3.375 mg/L), postoperative homocysteine (HCY) levels (OR=2.202, 1.268–3.826 μmol/L), history of diabetes (OR=1.955, 1.272–3.003), coronary bifurcation lesions (OR=3.785, 2.246–6.377), and stent length (OR=1.269, 1.179–1.365 mm) were independent risk factors of ISR after PCI (P<0.05).

Conclusions: Elevated hs-CRP and HCY levels after PCI, history of diabetes, coronary bifurcation lesions, and greater stent length were associated with a higher risk of ISR. Patients with a higher risk of ISR should receive routine follow-up and intense medication management after PCI to control the risk factors and to reduce ISR.

MeSH Keywords: Behavioral Risk Factor Surveillance System • Coronary Disease • Percutaneous Coronary Intervention

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Background

In recent years, with the rapid development of the economy, improvement of living standards, changes in lifestyles, and the adoption of unhealthy diets, coronary heart disease (CHD) has become the “first killer” that threatens human health [1,2]. One of every 6 deaths in the United States is caused by CHD. Approximately every 2 seconds, an American will have a coronary event, and approximately every minute, someone will die of such an event [3]. China has witnessed an alarming increase in the incidence of cardiovascular diseases (CVD). At present, China has a CVD population of about 290 million, among which 11 million have CHD [4]. In 2015, CHD was the leading cause of death among China’s urban and rural residents, and every 2 out of 5 deaths were related to CVD [5]. CHD has already become one of the biggest public health concerns in China.

Percutaneous coronary intervention (PCI) is a primary and common treatment for CHD [6-8]. Patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) with symptom onset to in-hospital first medical contact times of 3–6 h via inter-hospital transfer had better 1-year survival than those with in-hospital thrombolysis in the regional STEMI program [9]. Nicorandil intake before a PCI procedure can reduce the rate of no-flow phenomenon, reduce myocardial injury, and improve myocardial contractility [10]. A 5-year randomized controlled clinical study by Jung-Min Ahn indicated no significant difference in the incidence of major cardiovascular events between PCI and coronary artery bypass grafting (CABG) [11]. However, the incidence of in-stent restenosis (ISR) remains high. With bare-metal stents (BMS), the incidence of ISR was as high as 20–40% [12,13], and with drug-eluting stent (DES), the incidence still remained about 10% [14–17]. It is generally believed that ISR is one of the most important prognostic factors after PCI and is also one of the major difficulties in CHD treatment [18,19].

The factors affecting stent ISR after PCI have not been clearly defined. Many studies have discussed the factors influencing ISR, including the patient’s clinical factors, the vascular mechanical factors, the histology factors, and the molecular-level mechanism. Determining the risk factors of ISR after PCI, performing a risk stratification for the patients, taking intervention therapy or preventive measures, and reducing the incidence of postoperative ISR may be new directions of interventional therapy in the future. We performed the present retrospective case-control study to explore the risk factors for ISR.

Material and Methods

Subjects

We selected 1132 cases who received stent implantation at the Shaanxi People’s Hospital from June 2014 to June 2016 and were followed up by coronary angiography (CAG) within 6 to 12 months after PCI. There were 771 males (68.1%) and 326 females (31.9%), who were aged 35–83 (63.57±6.75) years old. The inclusion criteria were as follows: (1) confirmed CHD with stenosis ≥75% in at least 1 major coronary artery by CAG and having received PCI using drug-eluting stent; (2) receiving routine follow-up CAG within 6–12 months after PCI regardless of sex; (3) having complete clinical data. Exclusion criteria were: (1) coronary bifurcation lesions or severe calcification; (2) combined with myocarditis, pericarditis, myocardialopathy, congenital heart disease, valvular heart disease, and other structural heart disease; (3) lost to follow-up or not having received follow-up CAG within 1 year after PCI; (4) combined with immune system disease, infection, tumor, hematologic diseases, or severe liver and renal insufficiency. This research was approved by the Ethics Committee of Shaanxi Provincial People’s Hospital. Informed consent was signed by all patients, and they were all volunteers.

PCI and postoperative medication

All PCI procedures were undertaken by the same 2–3 experienced interventional cardiologists. Before emergency surgery, the patients were given 300 mg oral enteric-coated aspirin and 300 mg clopidogrel. Before selective surgery, the patients were given 100 mg/d aspirin and 75 mg/d clopidogrel for 3 consecutive days. During surgery, the patients assumed a supine position and received puncture of the radial artery or femoral artery using Seldinger technique. Infiltration anesthesia was performed subcutaneously using lidocaine at the puncture site. For anticoagulation, 8000–10 000 U heparin infusion (depending on body weight) was administered via the arterial sheath during surgery. Subcutaneous injection of 4000 IU low-molecular-weight heparin was performed twice daily for 3–5 days after surgery, along with 100 mg of oral aspirin once daily and 75 mg clopidogrel once daily for over 12 months. The treatment was considered successful if the residual stenosis of the lumen <10% was visually observed in at least 2 orthogonal projection positions, the lesioned vessel distal to the stent achieved TIMI grade 3 blood flow, and there were no severe complications related to surgery (e.g., myocardial infarction, sudden death, and emergency CABG).

Data collection

The following clinical data were collected: (1) baseline data: sex, risk factors of CHD (hypertension, hyperlipidemia, diabetes, obesity), age, and routine follow-up CAG within 6–12 months after PCI regardless of sex; (3) having complete clinical data. Exclusion criteria were: (1) coronary bifurcation lesions or severe calcification; (2) combined with myocarditis, pericarditis, myocardialopathy, congenital heart disease, valvular heart disease, and other structural heart disease; (3) lost to follow-up or not having received follow-up CAG within 1 year after PCI; (4) combined with immune system disease, infection, tumor, hematologic diseases, or severe liver and renal insufficiency. This research was approved by the Ethics Committee of Shaanxi Provincial People’s Hospital. Informed consent was signed by all patients, and they were all volunteers.

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Data collection

The following clinical data were collected: (1) baseline data: sex, risk factors of CHD (hypertension, hyperlipidemia, diabetes,
Follow-up CAG was performed using the Judkins technique [20]. ISR was defined as a reduction in the lumen diameter of the target vessel by over 50% after PCI (the proximal end and distal end, including the stent within 5 mm from the margin). The lumen diameter was determined by visual observation. Degree of restenosis was calculated as follows: degree of restenosis = lumen diameter at the stenotic position/normal value of the proximal lumen diameter at the stenotic position × normal value of the distal lumen diameter at the stenotic position/2 × 100% [21]. Using this criterion, 1132 cases were divided into the ISR group (n=93, 8.21%) and non-ISR group (n=1039, 91.78%) by follow-up CAG after surgery.

Based on the relationship between the degree of restenosis (length) and stent, the patients were classified using Mehran classification system [22]. ISR was divided into 4 classes, class: I, II, III, and IV. The flow chart of this study is shown in Figure 1.

**Statistical analysis**

Epidata 3.0 was used for double entry of the data. Statistical analyses were conducted using SPSS120.0 software. Count data are expressed as number of cases (n) and percentages (%), and measurements as mean±standard deviation (±s). Measurements were compared between the 2 groups by the t test, and counts were compared by the chi-square test (χ² test). Risk factors of ISR after PCI were identified by using binary multivariate logistic regression. Odds ratio (OR), P value, and 95% confidence interval (CI 95%) were calculated. P<0.05 indicated a significant difference.

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**Figure 1.** The flow chart of this study. PCI – percutaneous coronary intervention.
Results

Baseline data of ISR and non-ISR patients and univariate regression to screen risk factors

A total of 1132 CHD cases who received PCI were recruited. Follow-up CAG confirmed ISR in 93 cases, with the overall incidence of ISR of 8.21%. The left anterior descending (LAD) artery was affected in 33 cases (35.48%), left circumflex artery (LCX) was affected in 13 cases (13.98%), and right coronary artery (RCA) was affected in 47 cases (50.54%). According to Mehran classification, there were 11 (11.83%), 54 (58.06%), 21 (22.58%), and 7 (7.53%) cases of class I, II, III, and IV, respectively (Figure 2). Baseline data were compared between the ISR and non-ISR cases and risk factors of ISR were identified. The 2 groups showed no significant differences in age, sex, smoking history, history of alcohol abuse, hypertension, and family history of CHD (P>0.05). The percentages of ISR cases having a history of diabetes (45.16% versus 29.64%; \( \chi^2=9.623, P=0.002 \)) and a history of hyperlipidemia (41.94% versus 31.26%, \( \chi^2=4.466, P=0.035 \)) were significantly higher compared with the non-ISR cases (Table 1).

Univariate regression to screen laboratory indicators related to ISR

Univariate regression analysis was performed to screen laboratory indicators related to ISR. There were no significant differences in HDL-C, TC, TG, and Cr between ISR and non-ISR cases (P>0.05). However, the levels of LDL-C (3.25±0.57 vs. 2.94±0.53 mmol/L, t=5.25, P<0.001), the postoperative levels of hs-CRP (165.69±7.49 vs. 142.39±6.48 mg/L, t=32.75, P<0.001), HbA1c (8.07±1.33 vs. 6.91±1.14 mmol/L, t=9.284, P<0.001), UA (394.69±42.63 vs. 369.74±39.60 μmol/L, t=5.783, P<0.001), the postoperative levels of HCY (22.81±2.68 vs. 18.64±2.21 μmol/L, t=17.074, P<0.001) and Fib (3.14±0.53 vs. 2.95±0.45 g/L, t=3.937, P<0.001) were significantly higher in the ISR cases compared with non-ISR cases (Table 2).

Figure 2. ISR classification: According to Mehran classification (400×). (A) ISR type I; (B) ISR type II; (C) ISR type III (D) ISR type IV.
Univariate regression to screen CAG parameters and stent features related to ISR

CAG parameters and stent features were compared between ISR and non-ISR cases. The 2 groups showed no significant differences in the number of stents, target vessels affected by CHD, percentage of cases with multiple coronary arteries affected, and percentages of cases with diffuse lesions in the coronary artery (P>0.05). The stent diameter of the ISR cases (2.96±0.26 vs. 3.13±0.25 mm, t=-5.975, p<0.001) was much smaller compared with the non-ISR cases. Moreover, the stent length (26.43±3.40 vs. 24.01±3.26 mm, t=6.827, p<0.001) and the percentage of cases with coronary bifurcation lesions (24.73% vs. 7.99%; χ²=28.139, p<0.001) were significantly higher in ISR cases compared with non-ISR cases (Table 3).

Multivariate logistic regression to screen risk factors for ISR

After univariate regression, the risk factors of ISR were preliminarily screened. These risk factors included history of diabetes, hyperlipidemia, LDL-C, postoperative levels of hs-CRP, HbA1c, UA, HCY and Fib, stent diameter, stent length, and coronary bifurcation lesions. Multivariate logistic regression was conducted to exclude the confounding factors and to screen independent risk factors of ISR. Whether ISR occurred was

| Factors                          | ISR group (n=93) | Non-ISR group (n=1039) | χ²/t  | P    |
|----------------------------------|------------------|------------------------|-------|------|
| Age (years)                      | 63.06±8.58       | 66.62±6.56             | -0.757| 0.449|
| Male (n, %)                      | 58 (62.36%)      | 713 (68.62%)           | 1.539 | 0.215|
| History of smoking (n, %)        | 35 (37.63%)      | 332 (31.95%)           | 1.257 | 0.262|
| History of alcohol intake (n, %) | 22 (23.66%)      | 280 (26.95%)           | 0.473 | 0.492|
| History of hypertension (n, %)   | 61 (65.59%)      | 592 (56.8%)            | 2.595 | 0.107|
| History of diabetes (n, %)       | 42 (45.16%)      | 308 (29.64%)           | 9.623 | 0.002|
| History of hyperlipidemia (n, %)| 39 (41.94%)      | 326 (31.26%)           | 4.466 | 0.035|
| Family history of CHD (n, %)     | 10 (10.75%)      | 84 (8.08%)             | 0.798 | 0.372|

* P<0.05, compared with non-ISR cases. CHD – coronary atherosclerotic heart disease; ISR – in-stent restenosis.

Univariate regression to screen laboratory indicators related to ISR

Table 2. Univariate regression to screen laboratory indicators related to ISR (n=1132, ±s).

| Factors          | ISR group (n=93) | Non-ISR group (n=1039) | χ²/t  | P    |
|------------------|------------------|------------------------|-------|------|
| HDL-C (mmol/L)   | 1.04±0.26        | 1.07±0.19              | -1.087| 0.277|
| LDL-C (mmol/L)   | 2.52±0.57        | 2.94±0.53              | 5.250 | <0.001|
| TC (mmol/L)      | 4.47±1.29        | 4.39±1.08              | 0.800 | 0.462|
| TG (mmol/L)      | 1.95±0.83        | 2.02±0.67              | -0.791| 0.429|
| Postoperative hs-CRP (mg/L) | 165.69±7.49       | 142.39±6.48            | 32.750| <0.001|
| HbAl (mmol/L)    | 8.07±1.33        | 6.91±1.14              | 9.284 | <0.001|
| Cr (μmol/L)      | 78.23±11.37      | 76.39±10.23            | 1.507 | 0.132|
| UA (μmol/L)      | 394.69±42.63     | 369.74±39.60           | 5.783 | <0.001|
| Postoperative HCY (μmol/L) | 22.81±2.68        | 18.64±2.21             | 17.074| <0.001|
| Fib (g/L)        | 3.14±0.53        | 2.95±0.45              | 3.937 | <0.001|

* P<0.05, compared with non-ISR cases. HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; TG – triglyceride; hs-CRP – high-sensitivity C-reactive protein; HbA1c – glycosylated hemoglobin; Cr – urine creatinine; UA – uric acid; HCY – homocysteine; Fib – fibrinogen.

Multivariate logistic regression to screen risk factors for ISR

After univariate regression, the risk factors of ISR were preliminarily screened. These risk factors included history of diabetes, hyperlipidemia, LDL-C, postoperative levels of hs-CRP, HbA1c, UA, HCY and Fib, stent diameter, stent length, and coronary bifurcation lesions. Multivariate logistic regression was conducted to exclude the confounding factors and to screen independent risk factors of ISR. Whether ISR occurred was

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taken as the dependent variable and the risk factors of ISR were the independent variables. Binary multivariate logistic regression was used to screen the risk factors, and the regression model was established using backward Wald method. The inclusion level was set as 0.05 and the exclusion level was 0.10. Multivariate logistic regression indicated that postoperative hs-CRP (OR=2.309, 1.579-3.375 mg/L), postoperative HCY (OR=2.202, 1.268–3.826 μmol/L), history of diabetes (OR=2.202, 1.268–3.826), coronary bifurcation lesions (OR=3.785, 2.246–6.377), and stent length (OR=1.269, 1.179–1.365 mm) were independent risk factors of ISR after PCI, See Table 4.

**Table 3.** Univariate regression to screen CAG parameters and stent features related to ISR (n=1132, \( \chi^2 \pm \text{s/n, \%} \)).

| Factors                              | ISR group (n=93) | Non-ISR group (n=1039) | \( \chi^2/t \) | P     |
|--------------------------------------|------------------|------------------------|----------------|-------|
| Stent diameter (mm)                  | 2.96±0.26        | 3.13±0.25              | -5.975         | <0.001|
| Bracket length (mm)                  | 26.43±3.40       | 24.01±3.26             | 6.827          | <0.001|
| Number of stent implantation (n)     | 1.78±1.16        | 1.67±1.18              | 0.863          | 0.388 |
| Target vessel lesion site            |                  |                        | 3.891          | 0.143 |
| Left anterior descending branch (LAD)| 53 (56.99%)      | 509 (49.32%)           |                |       |
| left circumflex branch (LCX)         | 16 (17.20%)      | 156 (15.12%)           |                |       |
| Right coronary artery (RCA)          | 24 (25.81%)      | 214 (20.56%)           |                |       |
| multivessel disease (n, %)           | 45 (48.39%)      | 432 (41.58%)           | 1.623          | 0.203 |
| Coronary bifurcation lesion (n, %)   | 23 (24.73%)      | 83 (7.99%)             | 28.139         | <0.001|
| Coronary diffuse lesion (n, %)        | 11 (11.83%)      | 97 (9.34%)             | 0.614          | 0.433 |

Table 3.

**Table 4.** Multivariate logistic regression to screen risk factors of ISR (OR, 95%CI).

| Factors                              | B     | S.E   | Wald  | df  | Sig.   | Exp (B) | EXP(B) 95% CI  |
|--------------------------------------|-------|-------|-------|-----|--------|----------|-------------|
| Postoperative hs-CRP                 | 0.837 | 0.194 | 18.651| 1   | 0.000  | 2.309    | 1.579-3.375 |
| Postoperative HCY                    | 0.790 | 0.282 | 7.848 | 1   | 0.005  | 2.202    | 1.268-3.826 |
| History of diabetes                  | 0.670 | 0.219 | 9.350 | 1   | 0.002  | 1.955    | 1.272-3.003 |
| Coronary bifurcation lesion          | 1.331 | 0.266 | 24.998| 1   | 0.000  | 3.785    | 2.246-6.377 |
| Bracket length                       | 0.238 | 0.037 | 40.638| 1   | 0.000  | 1.269    | 1.179-1.365 |

Table 4.

hs-CRP – high-sensitivity C-reactive protein; HCY – homocysteine.

Discussion

PCI is a common interventional operation for the treatment of CHD. This operation can dilate the stenotic or obstructed coronary artery, relieve the clinical symptoms, and effectively rescue the critical condition [23,24]. ISR is a difficult problem in the treatment of CHD by PCI, and it is also a hotspot and difficult point of current research. At present, the pathogenesis of ISR after PCI is not fully understood. A recent report has proposed vascular intimal proliferation and infiltration of local inflammatory cells as the potential pathogenetic mechanism [25]. The further new atherosclerotic process is called “neoatherosclerosis” [26]. Here, we retrospectively reviewed the clinical data, laboratory indicators, CAG parameters, and stent features of CHD patients after PCI. Of the 1132 patients, stent restenosis was found in 93 cases, and the incidence of restenosis was 8.21%, consistent with related reports [14–17] in which the incidence of ISR was reported to be around 10%.

In this study, risk factors of ISR after PCI were screened from baseline data, coronary lesion-related factors, and stent-related factors. Univariate and multivariate logistic regression analysis verified that postoperative hs-CRP, postoperative HCY, history of diabetes, coronary bifurcation lesions, and stent length were independent risk factors of ISR after PCI.
hs-CRP is an inflammatory mediator in atherosclerosis and is considered as the most potent inflammatory marker of future cardiovascular and cerebrovascular events [27]. An elevated postoperative hs-CRP level indicates vascular inflammatory response, which increases the scope and instability of atheromatous plaques and leads to a hypercoagulable state. This may be a potential pathogenetic mechanism of ISR after PCI [28]. Our results demonstrated that the postoperative hs-CRP level was an independent risk factor of ISR after PCI. Hong et al. [29] arrived at a similar conclusion that a higher preoperative hs-CRP level was associated with a higher incidence of arterial restenosis compared with a normal hs-CRP level. Thus, determination of the pre-interventional hs-CRP level may help predict the development of restenosis after stenting. Postoperative hs-CRP level is also helpful to predict restenosis after stenting. From another perspective, proper control of postoperative hs-CRP can help to prevent restenosis.

Homocysteine (Hcy) is an intermediary amino acid formed by the conversion of methionine to cysteine. The increase of Hcy will have a direct or indirect effect on the gene expression of vascular endothelial cells, and then lead to the toxic effect of endothelial cells, leading to cell apoptosis. As a result, excess growth, proliferation, and fibrosis of arterial vascular smooth muscle cells may take place, which causes vascular endothelial thickening, impaired arterial elasticity, and in-stent formation of atherosclerotic plaques. This is considered as a potential pathogenetic mechanism of ISR. Hcy is an amino acid that can cause vascular injury [30]. De et al. [31] showed that patients with a moderately or severely elevated Hcy level might be at higher risk for restenosis and subacute thrombosis. Our study also indicated that the postoperative Hcy level was an independent risk factor of ISR after PCI. Early intervention for hyperhomocysteinemia to reduce preoperative and postoperative Hcy levels can help prevent ISR.

Diabetes is now recognized as an independent risk factor for CAD in CHD patients and is also a risk factor for ISR after PCI. The long-term hypercoagulable state, vascular endothelial metabolism, and dysfunction of coronary artery blood flow in diabetic patients can increase the risk of thrombosis [32–34]. Insulin can activate some growth factors to promote intimal hyperplasia, vascular smooth muscle cell proliferation and migration, and extracellular matrix deposition, and accelerate the formation of restenosis [35,36]. Our study verified that diabetes was an independent risk factor of ISR after PCI. Among 93 patients with ISR, 45.16% were combined with diabetes. Therefore, proper glycemic control is important for diabetic patients after PCI and deserves further study.

The characteristics of the coronary bifurcation lesions lead to the complicated surgical process, which can increase of the number of balloon dilatations and the use of the guide wires during stent implantation. Repeated balloon dilations and multiple wire applications can lead to aggravating vascular endothelial dysfunction on the original basis, resulting in an increased incidence of restenosis after stent placement [37,38]. It was verified in our study that coronary bifurcation lesions are an independent risk factor of ISR. Moreover, the longer the stent, the more severe the injury caused to the vessel, the stronger the inflammatory response, and the greater the intimal thickness. This further increases the risk of ISR. Stent length was another independent risk factor of ISR, which agrees with the research by Sun [39] and Alnimri et al. [40]. Therefore, an accurate estimate of lesion length and vascular diameter is the basis for determining the stent length and diameter, so that the stent can be precisely located and completely cover the lesion.

Conclusions

Postoperative levels of hs-CRP and Hcy, history of diabetes, coronary bifurcation lesions, and stent length are independent risk factors of ISR after PCI. Continuous monitoring and intense medication management to control risk factors are needed for patients carrying these risk factors to reduce ISR after PCI. Prospective clinical trials with a large sample size and at multiple centers are needed to elucidate the pathogenesis and high-risk factors of ISR.

Conflict of interest

None.

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