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Risk factors for in-stent restenosis after coronary stent implantation in patients with coronary artery disease

A retrospective observational study

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Abstract

To explore the risk factors for in-stent restenosis (ISR) after stent implantation in patients with coronary heart disease (CHD) using logistic regression analysis. From February 2020 to February 2022, 350 patients with CHD after percutaneous coronary intervention (PCI) were divided into a stent stenosis group and a stent nonstenosis group based on coronary angiography results performed 2 years after PCI. Univariate and multivariate logistic regressions were used to analyze the factors related to ISR after coronary stent implantation in patients with CHD. This study was approved by the Ethics Committee of Shandong University of Traditional Chinese Medicine. Patient signed informed consent. Of the 350 patients with CHD, 138 (39.43%) had stent restenosis while 212 did not. Univariate analysis showed that a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, discontinuation of aspirin, use of conventional dose statins, calcified lesions, ≥ 3 implanted stents, stent length ≥ 30 mm, stent diameter < 3 mm, and tandem stent increased the risk of restenosis. The incidence of restenosis was higher in the stent group than that in the nonstent group ($P < .05$). There were no significant differences in the blood lipid level, left ventricular ejection fraction, clopidogrel/ticagrelor or beta-blocker withdrawal, location of culprit vessels, and thrombotic lesions between the 2 groups ($P > .05$). Multivariate logistic regression analysis showed that family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, aspirin withdrawal, use of conventional doses of statins, calcified lesions, ≥ 3 implanted stents, stent length ≥ 30 mm, stent diameter < 3 mm, and tandem stenting were risk factors for ISR within 2 years after PCI. A family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, discontinuation of aspirin, use of conventional dose statins, calcified lesions, ≥ 3 stent implantations, stent length ≥ 30 mm, stent diameter < 3 mm, and tandem stenting are risk factors for ISR within 2 years after PCI in patients with CHD.

Abbreviations: CHD = coronary heart disease, ISR = in-stent restenosis, NSETMI = non-ST segment elevation myocardial infarction, PCI = percutaneous coronary intervention.

Keywords: coronary artery disease, influencing factors, logistic regression analysis, percutaneous coronary stent implantation, stent restenosis

1. Introduction

With the arrival and aggravation of an aging society, the morbidity of coronary atherosclerotic heart disease (CHD) has increased annually in recent years, becoming a common cardiovascular presentation in the clinic. CHD has a high incidence and mortality rate and poses a great threat to human life and health.[1,2] Coronary stent implantation has high safety and low surgical trauma, can promote the postoperative recovery of patients, and can achieve good therapeutic effects; therefore, it plays an important role in the clinical application of CHD.[3] Studies have shown that patients with CHD are prone to coronary artery in-stent restenosis (ISR) after stent implantation, with an incidence of 5 to 30%, which has a significant impact on the therapeutic effect and patient prognosis.[4]

With the increasing morbidity of CHD, percutaneous coronary intervention (PCI) is increasingly being carried out, and ISR is also receiving more attention after PCI.[5] ISR is one of the common complications after PCI and has been studied from

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The datasets generated during and/or analyzed during the current study are publicly available.

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the aspects of drug and stent type and implantation skills.[6,7] However, with the rapid development of PCI and the wide application of intravascular ultrasound, the indications for PCI are expanding with a concurrent increase in ISR incidence. Moreover, the mechanism of ISR remains unclear, with many factors reportedly being involved in its occurrence and development.[8] In this study, we aimed to investigate the factors influencing ISR occurrence in patients with CHD within 2 years of PCI to provide a reference for the prevention and treatment of ISR.

2. Materials and methods

2.1. General information

The clinical data of 350 patients with CHD who underwent PCI at our hospital from February 2020 to February 2022, including sex, age, and body mass index, were retrospectively studied. Clinical diagnosis (ST-segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, unstable angina), mean arterial pressure, family history of CHD, history of type 2 diabetes mellitus, hypertension, smoking, and drinking, serum concentrations of total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, left ventricular ejection fraction, discontinuation of enteric-coated aspirin, clopidogrel bisulfate, ticagrelor, and beta blockers, statin dosage, and other information were collected. The coronary angiography and intervention results were also recorded. The number of diseased vessels (single-vessel, double-vessel, multivessel), culprit vessels (left anterior descending, left circumflex, or right coronary artery), lesion types (calcified or thrombotic lesion), number of stents implanted, stent length and diameter, and tandem stenting occurrence were also collected.

2.2. ISR diagnostic criteria

ISR[9] was defined as when coronary angiography after stent implantation showed that the 2 edges of the stent were 5 mm or the inner diameter of the stent was ≥ 50% of the lumen area.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: ISR diagnosis was met; general patient information was complete; the patient underwent coronary stenting or drug-eluting stent implantation for the first time at our hospital; the patient was on antiplatelet drugs for at least 1 year; and the patient underwent coronary angiography again at our hospital.

The exclusion criteria were as follows: severe hepatic and renal dysfunction; first stent implantation in other hospitals; lack of general information; bare stent implantation; postcoronary artery bypass grafting; severe bleeding tendencies or hematological diseases; and gastrointestinal bleeding, malignant tumors, and other critical diseases.

2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 26.0; IBM, Chicago, IL). Counting data are expressed as cases, and x^2 tests were used for group comparisons. Measurement data in line with normal distribution are expressed as ($\bar{x}$ ±s), t test was used for comparison between the groups, and logistic regression analysis was used for multivariate analysis. Statistical significance was set at $P < .05$.

3. Results

3.1. Comparison of general information

The 350 patients with CHD were divided into a stent stenosis group (n = 138) and a stent non-stenosis group (n = 212) according to whether restenosis occurred after surgery. There was no significant difference in the general data between the 2 groups ($P > .05$) (Table 1).

3.2. Univariate analysis of ISR after coronary stent implantation

Univariate analysis showed that a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, withdrawal of aspirin, use of conventional doses of statins, calcified lesions, ≥ 3 implanted stents, stent length ≥ 30 mm, and stent diameter < 3 mm increased the restenosis incidence in the coronary stent group than in the non-stent group ($P < .05$). There were no significant differences in the blood lipid levels, left ventricular ejection fraction, clopidogrel/ticagrelor or beta-blocker withdrawal, location of culprit vessels, and thrombotic lesions between the 2 groups ($P < .05$) (Table 2).

3.3. Logistic regression analysis of restenosis after coronary stent implantation

The occurrence of ISR within 2 years of PCI was considered the dependent variable (yes = 1, no = 0). The relevant indices with

Table 1

Comparison of patient characteristics between the 2 groups.

	Stent stenosis group (n = 138)	Stent nonstenosis group (n = 212)	χ^2/t value	*P* value
Sex (male/female, n)	71/67	97/115	1.086	.297
Average age ($\bar{x}$ ±s, years)	68.23 ± 8.67	69.15 ± 9.04	−0.945	.345
BMI ($\bar{x}$ ±s, kg/m^2)	23.14 ± 1.17	23.06 ± 1.02	0.676	.499
Clinical diagnosis (n)			0.342	.843
STEMI	54	78		
NSTEMI	41	69		
UA	43	65		
Mean arterial pressure ($\bar{x}$ ±s, mm Hg)	99.46 ± 12.31	99.17 ± 11.97	0.219	.827
Number of diseased branches			4.828	.089
Single vessel	44	92		
Two vessel	61	81		
Multivessel	33	39		

NSETMI = non-ST segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction, UA = unstable angina.

Table 2

Univariate analysis of restenosis after coronary stent implantation.

			Stent stenosis group (n = 138)	Stent nonstenosis group (n = 212)	χ^2/t value	*P* value
Family history of CHD (n)	Yes		97	169	4.073	.044
	No		41	43		
History of type 2 diabetes (n)	Yes		99	114	11.326	.001
	No		39	98		
History of hypertension (n)	Yes		126	176	4.849	.028
	No		12	36		
Smoking history (n)	Yes		91	97	13.701	.000
	No		47	115		
Drinking history (n)	Yes		63	67	7.066	.008
	No		75	145		
Lipid levels ($\bar{x}$ ±s, mmol/L)	TC		3.54 ± 0.73	3.66 ± 0.78	-1.442	.150
	TG		1.31 ± 0.47	1.25 ± 0.41	1.262	.208
	HDL-C		1.13 ± 0.14	1.15 ± 0.17	-1.151	.251
	LDL-C		2.24 ± 0.76	2.16 ± 0.33	1.350	.178
LVEF (n)	<50%		61	88	0.248	.618
	≥50%		77	124		
Aspirin discontinuation (n)	Yes		24	15	8.984	.003
	No		114	197		
Clopidogrel/ticagrelor discontinuation (n)	Yes		63	118	3.353	.067
	No		75	94		
Beta-blockers discontinuation (n)	Yes		16	19	0.643	.422
	No		122	193		
Dosage of statins (n)	Regular dose		76	75	13.218	.000
	Double dose		62	137		
Culprit vessel (n)	LAD		61	103	5.832	.054
	LCX		24	52		
	RCA		53	57		
Classification of lesions (cases)	Thrombosis	Yes	102	151	0.301	.583
		No	36	61		
	Calcified lesions	Yes	61	122	5.966	.015
		No	77	90		
Number of stents implanted (n)	< 3		54	116	8.129	.004
	≥ 3		84	96		
Stent length (n)	< 30 mm		109	128	13.239	.000
	≥ 30 mm		29	84		
Stent diameter (n)	< 3 mm		48	111	10.416	.001
	≥ 3 mm		90	101		
Tandem stent (n)	Yes		27	85	16.189	.000
	No		111	127		

CHD = coronary heart disease, HDL-C = high-density lipoprotein cholesterol, LAD = left anterior descending, LCX = left circumflex, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, RCA = right coronary artery, TC = total cholesterol, TG = triglyceride.

statistical significance in the univariate analysis (Table 2) were taken as independent variables (variable assignment: yes = 1, no = 0) for the multivariate logistic regression analysis. The results showed that a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, discontinuation of aspirin, use of conventional doses of statins, calcified lesions, stent number ≥ 3, stent length ≥ 30 mm, stent diameter < 3 mm, and tandem stenting were risk factors for ISR within 2 years of PCI (Table 3).

Table 3

Logistic regression analysis of restenosis after coronary stent implantation.

Project	Beta value	SE value	Wald x^2 values	*P* value	OR (95% CI)
Family history of CHD	2.372	0.465	24.647	<.001	1.524 (1.184–2.519)
History of type 2 diabetes	1.531	0.427	9.412	<.001	1.922 (1.715–3.401)
History of hypertension	1.729	0.363	30.228	<.001	1.783 (1.349–2.158)
Smoking history	1.463	0.681	26.401	<.001	1.981 (1.281–3.744)
Drinking history	0.915	0.259	5.207	.002	2.983 (1.427–4.952)
Aspirin discontinuation	1.853	0.955	4.084	.025	1.715 (1.172–2.451)
Use of conventional dose of statin	2.753	0.447	40.876	<.001	1.438 (1.092–3.879)
Calcified lesions	0.669	0.154	5.258	.017	4.4583 (1.178–6.285)
Number of stents ≥ 3	1.275	0.622	4.226	.004	2.191 (1.068–4.173)
Stent length ≥ 30 mm	2.374	0.576	17.233	<.001	1.524 (1.147–2.813)
Stent diameter < 3 mm	2.756	0.732	30.147	<.001	1.437 (1.107–3.036)

CHD = coronary heart disease, OR = odds ratio.

4. Discussion

ISR is a common clinical complication after PCI. With the rapid development of PCI, its indications are expanding, with a concurrent increase in ISR incidence.[10] However, the mechanism of ISR remains unclear and is a complex pathological process. Some studies have shown that the ISR incidence after stent implantation is related to several aspects, such as inflammation, vascular remodeling, vascular elastic recoil, smooth muscle cell proliferation and migration, thrombosis, and extracellular matrix accumulation.[11] In addition, some studies suggest[12] that ISR will not lead to serious consequences; the patients are relatively stable and good clinical efficacy can be achieved after the second coronary intervention. However, with the development of coronary intervention in recent years, the number of stent implantations has increased annually. Furthermore, the number of acute myocardial infarctions or sudden deaths caused by ISR is also increasing; therefore, clinical workers should pay attention to ISR.

The study showed that 138 of the 350 patients with CHD had bleeding stent restenosis, with an incidence of 39.43%. Studies have shown[13–15] that metabolic and genetic factors, poor living habits, and stent-related factors (number, length, diameter, etc.) are the main factors affecting ISR occurrence. The results of the univariate analysis showed that patients with a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, ≥ 3 implanted stents, stent length ≥ 30 mm, stent diameter < 3 mm, tandem stenting, conventional dose of statins, withdrawal of aspirin, and calcified lesions had a higher incidence of ISR. Logistic regression analysis revealed that a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, discontinuation of aspirin, conventional doses of statins, calcified lesions, ≥ 3 implanted stents, stent length ≥ 30 mm, stent diameter < 3 mm and tandem stenting were risk factors for ISR within 2 years of PCI.

The incidence of thrombosis in patients with a family history of CHD is higher than that in patients without a family history of CHD, which may be related to immune and genetic factors.[16] Therefore, patients with a family history of CHD should be more alert to thrombosis risk and the timely and rational use of drugs for intervention. Abnormal metabolism in the body is a major cause of damage to the coronary artery endothelium. The high ICR incidence after PCI in patients with diabetes mellitus may be closely related to the role of insulin in the proliferation and migration of smooth muscle cells, the imbalance between the coagulation and anticoagulation systems, and the weakening of the relaxation–contraction function of endothelial cells. The occurrence of hypertension can lead to further aggravation of coronary endothelial injury. When systolic blood pressure increases by 10 mm Hg, the incidence of ISR can increase by approximately 20%. Some patients with CHD undergoing stent implantation have a history of hypertension; individuals with hypertension are twice as likely to develop coronary atherosclerosis.[17] The incidence of ISR after stent implantation in patients with a history of smoking and drinking is reportedly twice as high as that in those without such a history.[18] Smoking and drinking can cause coronary artery spasms and vascular endothelial cell damage, leading to atherosclerosis and platelet adhesion. Increased fibrinogen levels can further lead to thrombosis, which increases the risk of long-term mortality in patients with CHD. This study showed that the number of stents implanted, stent length and diameter, and presence of tandem stenting were predictive factors of ISR after stent implantation in patients with CHD. Stent implantation can lead to different degrees of inflammation and induce endothelial proliferation; therefore, a stent with a smaller length and large diameter should be selected and should not be connected in series as far as possible. Discontinuation of aspirin increases the risk of platelet aggregation, and a shorter antiplatelet time increases the risk of stent restenosis. Statins can effectively reduce the concentration of low-density lipoprotein cholesterol, stabilize plaques, reverse plaque formation, and improve the inflammatory response, thus playing an important role in improving the prognosis of patients with CHD. The selective use of large doses of statins can increase the plasma concentration of statins, which greatly reduces the occurrence of ISR. However, it should be noted that we should always be alert, when prescribing large doses of statins in the clinic, to the possible adverse reactions, such as liver damage and muscle pain.[19] Calcified lesions are more serious in blood vessels, making it difficult for the guide wire to pass through the diseased vessel during coronary angiography. Additionally, it is more difficult for the stent to adhere to the wall, resulting in a higher risk of stent restenosis.

The study had some limitations: the sample size was small and it was a single-center retrospective study; asymptomatic patients without follow-up coronary angiography were not included in this study, which may have led to the omission of some patients with restenosis without clinical signs and symptoms; and this study did not account for the types and classifications of drug-eluting stents implanted in patients; therefore, it was impossible to analyze the impact of different drug-eluting stents on ISR.

In summary, a family history of CHD, history of type 2 diabetes, hypertension, smoking, and drinking, discontinuation of aspirin, use of conventional doses of statins, calcified lesions, ≥ 3 implanted stents, stent length ≥ 30 mm, stent diameter < 3 mm, and tandem stenting were risk factors for ISR in patients with CHD within 2 years of PCI. However, due to the limitations of this study, further large scale and multicenter studies are needed to analyze the clinical characteristics and pathogenesis of ISR to provide a reference for individualized treatment strategies.

There are many factors closely related to ISR. which can be divided into 3 parts: First, the risk factors of patients themselves; Second, related factors of coronary artery disease; Third, surgical related factors. Self-risk factors include diabetes mellitus, smoking history, poor blood pressure control, irregular use of antiplatelet and statins after stent implantation may be closely related to the occurrence and development of ISR. Diabetes patients with insulin resistance, blood glucose, increased blood viscosity, blood flow slowed, sugar metabolic abnormalities can induce vascular intima inflammation, led to increasing protein glycosylation and oxidation process, the formation of atherosclerosis, also play an important role in the process, and can lead to endothelial injury, these may be the cause of a higher risk of ISR. Smoking can cause vascular endothelial damage, induce arterial spasm, cause arterial blood supply insufficiency, promote atherosclerosis, slow down blood flow, aggravate the risk of thrombosis, and stent restenosis. Smoking cessation can significantly reduce the incidence of ISR. Elevated blood lipids can cause damage to vascular endothelial cells, which is the initiating factor of atherosclerosis. Damage to endothelial cells promotes the occurrence and development of atherosclerosis, and these factors will increase the risk of ISR after surgery. The lesion reference diameter ≥ 3 mm is a protective factor for ISR, which may be because the lesion reference diameter less than 3 mm requires greater release pressure during stent implantation, and the damage to the integrity of vascular endothelial cells is more obvious. The longer the vascular diameter of the primary lesion, the smaller the diameter. For complex lesions such as calcification, bending, complete occlusion, and severe degree of coronary artery disease, the placement of multiple stents and stent fracture during the operation can increase the possibility of ISR. The implantation of multiple stents is associated with restenosis, which may be due to the slow blood flow in diffuse lesions. Multiple stents increase the total area of contact between the stent body and the vessel wall, leading to the proliferation of neointima and increasing the restenosis rate. The lesions with small stent diameter and long stent length have slow blood flow and increased contact area, thus increasing the probability of thrombosis.

Coronary stents have a high clinical application rate in China, and with the increasing incidence of CHD, related studies on their application are increasing. The effect of coronary stents is affected by many factors, among which restenosis in coronary stents is a kind of adverse condition that seriously affects the effect and prognosis of coronary stents. The prevention and control of ISR is the focus of this study. The understanding of the influencing factors of restenosis in coronary stents is an important reference for the formulation of intervention measures. Clinical studies related to restenosis are common and involve a wide range of influencing factors. However, there are many differences and deficiencies in the studies, which lead to the lack of reference for the formulation of comprehensive intervention measures. Therefore, this study conducted a detailed study on the incidence of coronary stent restenosis and its influencing factors. Besides, As a traditional Chinese medicine hospital, we can formulate a traditional Chinese medicine treatment plan according to the influencing factors of ISR, and use traditional Chinese medicine decoction, acupuncture and other treatment methods to prevent the occurrence of coronary stent restenosis in future clinical research.

Author contributions

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