Occurrence and predictive risk factors associated with in-stent restenosis after drug-eluting stent implantation in diabetic patients: a prospective, clinical cohort study

ShengGang Zhao

the second affiliated hospital of JiaXing University <https://orcid.org/0000-0001-6716-2408>

Jian-Jiang Xu

The second affiliated hospital of JiaXing University

Li-Qin Jiang

The second affiliated hospital of Jiaying University

Zhen-Liang Chu

the second affiliated hospital of Jiaying University

An-Qian Tao

Jiaying University

Lei Jin

Jiaying University

Ji-Bo Han

the second affiliated hospital of JiaXing University

Bin Zhang

the second affiliated hospital of JiaXing University

Zhan-Xiong Zheng

the second affiliated hospital of JiaXing University

Feng-Jie Shi

the second affiliated hospital of JiaXing University

Ran Zhang

the second affiliated hospital of JiaXing University

Xiang-Yu Zhang

the second affiliated hospital of JiaXing University

Fen-Fen Jiang

the second affiliated hospital of JiaXing University

Bing-Jiang Han (✉ Hanbingjiangjx@hotmail.com)

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Abstract

Background

The incidence of in-stent restenosis (ISR) in patients with diabetes mellitus (DM) after percutaneous coronary intervention (PCI) is significantly higher than that in patients without DM, but the mechanism is not clear. We hypothesised that patients with and risk factors including dyslipidaemia, elevated inflammatory factors would be prone to induction of ISR, and that dynamic observation of the comprehensive risk factor changes before and after PCI would be helpful to identify ISR .

Methods

This prospective cohort study consecutively enrolled 360 patients who received coronary drug-eluting stent implantation. Patients who underwent coronary angiography (CAG) and received clinical follow-up were prospectively reviewed. The patients were assigned to a DM (262) or a non-DM (98) group. The patients were further assigned according to whether ISR was present to the non-DM + non-ISR, non-DM + ISR, DM + non-ISR, and DM + ISR groups. The patients were further assigned according to whether low-density lipoprotein (LDL-c) was decreased more than 50% compared with baseline, or was less than 1.80 mmol/L in the follow-up, to the LDL-c achieved or the LDL-c failure groups.

Results

DM patients were prone to develop ISR after PCI and the degree of coronary stenosis was more severe than in non-DM patients. This result was more striking in DM and LDL-c failure patients. The levels of total cholesterol (TC), triglyceride, high-density lipoprotein (HDL-c), LDL-c, apolipoprotein B100, apolipoprotein E, remnant lipoprotein, TC/HDL-c ratio and triglyceride/HDL-c ratio in the DM + non-ISR were similar to those in the DM + ISR group before PCI and CAG. .The DM + ISR group had the highest levels of haemoglobin A1c and the highest Gensini scores. The inflammatory index changes including leukocytes and neutrophils were the most striking in the DM + ISR group. In multivariate regression analysis, neutrophil changes and glycosylated haemoglobin were independent risk factors for ISR [Δ neutrophil, OR 1.929,95% CI 1.216–3.058; HbA1-c OR 1.559,95% CI 1.001–1.707].

Conclusion

Coronary artery disease patients with DM had a high risk for ISR if they had preoperative risk factors including dyslipidaemia, elevated inflammatory factors, and a high Gensini score. Dynamic observation of the changes of the preoperative and postoperative comprehensive risk factors was helpful to identify ISR in patients with DM.

Background

Percutaneous coronary intervention (PCI) is the most commonly used clinical method for the treatment of coronary atherosclerosis [1]. However, in-stent restenosis (ISR) has become a thorny problem in clinical practice. Although several large clinical trials showed that drug-eluting stents (DES) could significantly reduce the rate of ISR [2], the incidence of ISR after DES has remained at 5% -10%. Despite the adoption of new drugs and revascularisation strategies, ISR after PCI remains a major obstacle for interventional cardiology

ISR is defined as a gradual re-narrowing of a stented lumen due to arterial damage and subsequent tissue proliferation. The ISR definition is further divided into coronary angiography (CAG) ISR and clinical ISR [3]. The ISR defined by CAG is a lumen diameter that is reduced by 50% or more in the stent, or within 5 mm of the periphery of the stent, as determined by follow-up angiography after PCI [2, 3]. Clinical ISR is defined based on the presence of a 50% or more reduction in the coronary artery lumen diameter within 5 mm of the stent implantation or the periphery of the stent, and when one or more of the following conditions is also present: evidence of objective ischaemia (electrocardiogram changes); history of recurrent angina; coronary fractional flow reserve value < 0.8; intravascular ultrasonography detected minimum cross-sectional vascular area < 4 mm² (Left trunk < 6 mm²); and restenosis that exceeds more than 70% reduction in the diameter of the lumen even without obvious symptoms [3].

As coronary stents have evolved from bare metal stents (BMS) to DES, then to subsequent DES iterations, the incidence of ISR has gradually decreased. J-Cypher research focused on the adverse reactions of the first generation DES and enrolled 12,812 patients who received sirolimus-eluting stent treatment [3]. Among these patients, the 1-year target lesion revascularisation rate was 7.3%, at 5 years it

was 15.9%, and the annual incidence rate was 2.2% [4]. Compared with the first generation DES, the incidence of all-cause death and myocardial infarction in the second-generation DES was significantly reduced [5]. However, in the first and second generations of DES, there was a late catch-up phenomenon of endometrial hyperplasia, which resulted in a significant increase in the incidence of late occurring ISR [1]. The reason why the incidence of ISR has increased significantly in recent years may be that patients with complicated and serious coronary artery disease received PCI treatments, and had high Syntax scores, which caused a significant increase in the restenosis rate [1, 2, 6].

Patients with DM have a significantly higher percentage of ISR after PCI than that of patients without DM. The mechanism may be that diabetes can lead to an abnormal function of the vascular endothelium and smooth muscle cells, which can promote thrombosis and platelet aggregation [7, 8], hyperglycaemia, excessive free fatty acid release, insulin resistance, and an exacerbation of vascular endothelial dysfunction. These factors can lead to increased activity of proinflammatory transcription factors, overexpression of leukocyte adhesion molecules, and the production of chemokines and cytokines. Hyperglycaemia can enhance the activity of advanced glycation end products, thereby accelerating vascular inflammation, promoting smooth muscle cell proliferation and extracellular matrix production, and ultimately lead to excessive intimal hyperplasia and restenosis [8]. In addition, due to diabetic atherosclerosis, which is often complicated by insufficient vascular compensatory remodelling, patients with DM often have blood vessels with small diameters [9]. Insufficient stent expansion is also a mechanism for the formation of diabetic ISR [10, 11]. In addition, dyslipidaemia is common in patients with DM, and is characterised by high triglyceride (TG) and VLDL-c levels, along with normal LDL-c levels [12].

At present, there are many studies that have examined ISR and baseline blood lipid composition, but there are few studies that have focused on the predictive value of blood lipid composition changes and the development of ISR. In addition, dyslipidaemia is closely related to the inflammatory response, and is clearly correlated with ISR. Because patients with DM often have dyslipidaemia and hyperinflammation, further exploration of the comprehensive risk factors regarding the occurrence of ISR in DM, and the identification of possible targets and prediction models is necessary. Several studies have focused on the level of risk factors at baseline before PCI to predict ISR, and few studies examined the changes in the levels of lipids, glucose, and inflammation to explore ISR in patients with DM. Furthermore, most previous studies were retrospective. Additionally, the interaction relationship of many risk factors for stent restenosis was not clear. We therefore hypothesised that 1) patients with coronary artery disease who had risk factors including dyslipidaemia, elevated inflammatory factors, and high Gensini scores would be prone to develop ISR, and 2) that dynamic observation of the changes of comprehensive risk factors before and after PCI would be helpful for the early identification of ISR in patients with DM.

Methods

Study population

This prospective clinical cohort study continuously enrolled stable angina or acute coronary syndrome patients who underwent DES implantation, and who were expected to undergo CAG repeated in clinical follow-up in the Department of Cardiology at the the second affiliated hospital of Jiaying University from January 2012 to December 2017. The aim of the study was to determine whether patients with coronary artery disease who had risk factors including dyslipidaemia, elevated inflammatory factors, and high Gensini scores would be more likely to develop ISR, and to determine if the dynamic observation of the changes of comprehensive risk factors before and after PCI would be helpful for the early identification of ISR in patients with DM.

The inclusion criteria were: (1) patients older than 18 years; (2) patients who were diagnosed in accordance with the diagnostic criteria for coronary intervention therapy [13]; (3) patients with an initial stent treatment; (4) patients with a successful stent implantation, and residual stenosis that was less than 20%; (5) patients who experienced no serious complications during the operation and hospitalisation; and (6) long-term (at least one year) tolerance of dual antiplatelet drugs, and statin therapy after discharge.

The exclusion criteria were: (1) patients with a previous history of coronary stent treatment and coronary artery bypass grafting; (2) patients with a previous restenosis after coronary drug balloon therapy; (3) patients with a history of malignant tumour, abnormal liver and kidney function, or with infectious diseases or acute and chronic active inflammation; (4) patients who were allergic to aspirin, clopidogrel, statins, heparin and other drugs; and (5) patients who had a history of haemolytic diseases, rheumatism, and thyroid hormone abnormalities.

Because this was a prospective study, all subjects were required to sign an informed consent form. The study complied with the Declaration of Helsinki and was approved by the ethics committee of the second affiliated hospital of Jiaying University.

Research plan

Grouping

According to the exposure factors for DM, all patients were assigned to the combined DM group or to the non-combined DM group. The patients' baseline parameters included age, sex, the presence of risk factors related to CHD (DM, hypertension, dyslipidaemia, family history, and smoking), fasting blood glucose, thyroid function, blood electrolytes, blood lipid profile, left ventricular ejection score (LVEF), and cardiac ultrasound results were collected. Hypertension was defined as a history of systolic blood pressure (SBP) > 140 mmHg and / or diastolic blood pressure (DBP) > 90 mmHg. DM was defined by fasting blood glucose test results of at least 126 mg / dl and / or the use of insulin or other antidiabetic drugs.

Fasting venous blood was tested before PCI and before repeated CAG in follow-up. The specific indicators included: TC, TG, LDL-c, HDL-c, RPL-C (TC minus low-density lipoprotein and high-density lipoprotein), non-HDL-c (TC minus high-density lipoprotein), ApoA1, ApoB100, ApoE, uric acid (UC), creatinine (Ccr), blood calcium concentration, blood magnesium concentration, blood phosphorus concentration, homocysteine (Hcy), Glycated haemoglobin A1c (HbA1c), C-reactive protein (CRP), white blood cell (WBC), neutrophil (N), lymphocyte (L), monocyte (M), red blood cell (RBC), haemoglobin (Hb), platelet value (PLT), RBC distribution width (RDW), and platelet distribution width (PDW).

Interventional treatment of coronary heart disease

Patients who underwent elective interventional therapy were administered aspirin 0.1 g, clopidogrel 75 mg, and atorvastatin 20 mg once a day 48 hours before surgery. Emergency intervention patients were administered aspirin 0.3 g, clopidogrel 600 mg and atorvastatin 40 mg once as a loading dose. We followed the standardised procedures for interventional treatment guidelines for stable CHD and unstable coronary heart disease^[13]. The criteria for successful stent implantation included: complete stent expansion, residual stenosis <20%; no obvious damage to the proximal and distal vessels of the stent; and thrombolysis in myocardial infarction (TIMI) blood flow level 3. The PCI-related DES stent diameter, the length and balloon inflation pressure, and the postoperative standardised medical treatment were recorded.

The Gensini score was calculated based on the severity of coronary stenosis as shown by CAG as follows: 1% to 25% coronary stenosis was scored as one point, 26% to 50% stenosis was two points, 51% to 75% stenosis was four points, 76% to 90% was eight points, 91% to 99% was 19 points, and 100% complete occlusion was 32 points. The coefficients of the corresponding lesions and branch vessels were assessed as follows: 5 points for the left main trunk, 2.5 points for the anterior descending branch, 1.5 points for the middle segment, 1.5 points for the distal segment, 1 point for the first diagonal branch, 1 point for the second diagonal branch, 2.5 points for the proximal segment of the circumflex branch, 1 point for the distal segment, 1 point for the blunt margin branch, and 1 point each for the proximal segment of the right coronary artery, middle segment, distal segment, posterior descending branch, and posterior branch of the left ventricle. All the lesions were identified, then they were multiplied by the corresponding coefficient; the integrated score was the total Gensini score. The Gensini score (no-stent) was the total Gensini score minus the coronary with stent implantation Gensini score. The participants were assigned to the LDL-c achieved group or the LDL-c failure group according to whether LDL-c was decreased by more than 50% compared with baseline or was less than 1.80 mmol/L in the follow-up.

Clinical follow-up and CAG

After being discharged from the hospital, the patients were followed up by telephone or an outpatient clinic visit once a month to record the health status, medication use, and to inquire about the side effects and symptoms the patients have experienced. The end point was set as restenosis in the stent.

The CAG results were routinely reviewed 1 year after PCI in the enrolled population. If patients experienced clinical symptoms (typical angina symptoms, positive exercise plate test, acute coronary syndrome, among others), they could elect to undergo a repeat CAG. Two independent interventional physicians interpreted the CAG results. If the results were inconsistent, three or more interventional physicians provided a joint interpretation. CAG was performed with a digital subtraction angiography system (Allura Xper FD-20 X-ray system; Philips Medical, Netherlands). CAG ISR was determined as follows: re-angiography revealed that the stent or the surrounding segments of the stent (within 5 mm of the two sides of the stent) lumen diameter was narrowed by more than 50%. If <50% stenosis was observed, it was interpreted as non-ISR.

Statistical analysis

We used SPSS statistical software package, version 22.0 (IBM, New York, United States) to conduct the statistical analyses. The data distribution was analysed by a Kolmogorov-Smirnov test. When a normal distribution was met, the continuous variable data was expressed

as a mean and standard deviation, and the non-normal data was expressed as a median (interquartile range). Continuous variables were tested using the independent Student test, Mann-Whitney U test or Wilcoxon rank sum test. The categorical variables were expressed as rates (%), and the chi-square test was used. Univariate and multivariate regression analysis was used to assess the association between the risk factors and ISR. The Receiver operating characteristic curve, (ROC) was used to determine the optimal cut-off value of the risk factors that could predict ISR. The Kaplan-Meier method was used to analyse the cumulative occurrence of ISR in the DM and non-DM groups, along with a log-rank calculation test. A two-sided P value <0.05 was determined to be statistically significant.

Results

Follow-up PCI population baseline and interventional treatment comparison

A total of 400 follow-up PCI patients were enrolled [non-diabetic group (n = 284),

diabetic group (n = 116)], 40 patients missing from follow-up, included 22 in the non-diabetic and 18 in the diabetic group (Supplementary additional file Fig. 1). Then total of 360 patients with follow-ups included 262 in the non-DM group and 98 in the DM group. Table 1 shows the disease composition in the non-DM and the DM groups (stable angina, acute coronary syndrome proportion), and left ventricular ejection fraction, left atrium diameter, stent length, average balloon dilation pressure, follow-up interval. There is no statistical difference in the data shown in Table 1. However, the DM group included more participants with hypertension compared to the non-DM group ($P < 0.05$). There were more patients in the DM group who did not achieve the systolic blood pressure control target compared to the non-DM group ($P < 0.05$). The DM group included fewer smokers (41/98) compared to the non-DM group (145/262) ($P < 0.05$).

Table 1
Comparison of baseline and interventional treatment in PCI population

	Non-DM(n = 262)	DM(n = 98)	P
Age (years)	63.89 ± 9.93	65.19 ± 10.63	0.268
Male, n (%)	196((74.81%)	62(63.27%)	0.031
Hypertension, n (%)	186((70.99%)	79(80.61%)	0.031
Systolic blood pressure mmHg	135.65 ± 21.57	141.22 ± 20.19	0.027
Diastolic blood pressure, mmHg	78.88 ± 12.87	80.38 ± 12.76	0.326
Smoking history, n (%)	145(55.34%)	41(41.84%)	0.022
Hyperlipidemia, n (%)	72(27.01%)	30(30.61%)	0.571
SAP	119	44	0.992
ACS	143	54	
LVEF(%)	61.50 ± 6.84	61.16 ± 7.63	0.718
LA(mm)	34.48 ± 5.10	35.07 ± 4.61	0.376
Stent target vessel position, n (%)			
Left anterior descending artery, n (%)	155(59.16%)	63(64.29%)	0.039
Right coronary artery, n (%)	60(22.90%)	29(29.59%)	
Left circumflex artery, n (%)	38(14.50%)	5(5.10%)	
Left main trunk, n (%)	9(3.44%)	1(1.02%)	
Stent diameter (mm)	3.00(1.50–4.00)	3.00(2.25–4.00)	0.127
Stent length (mm)	24.00(12.00–38.00)	12.00(12.00–38.00)	0.485
Average balloon inflation pressure, atm	15.00(8.00–26.00)	16.00(9.00–22.00)	0.148
Follow-up interval (months)	12.00(1.00–77.00)	12.00(1.00–72.00)	0.520
Data were expressed as mean ± SD, median with minimum and maximum or n (%)			
Note: SAP stable angina pectoris, ACS acute coronary syndrome, LVEF left ventricular ejection fraction, LA left atrium.			

Comparison of the incidence of intra-stent restenosis at the end of follow-up

ISR accounted for 20/98 vs 27/262 in the DM and non-DM populations, respectively ($P < 0.05$) (Supplementary additional file Fig. 2). Therefore, according to the history of DM and whether ISR occurred, participants were assigned to the non-DM + non-ISR group ($n = 235$), non-diabetes + ISR group ($n = 27$), DM + Non-ISR group ($n = 78$), and DM + ISR group ($n = 20$).

The patients' baseline characteristics and disease composition were similar in the four groups. However, in the two groups with DM (DM + non-ISR, and DM + ISR), the proportion of patients with hypertension was higher than that of the non-DM groups (non-DM + non-ISR, and non-DM + ISR) ($P < 0.05$). The proportion of patients with hypertension was highest in the DM + ISR group (85%). In terms of systolic blood pressure, more patients in the DM + ISR and the DM + non-ISR groups failed to reach the systolic blood pressure control target when compared to the corresponding non-DM + ISR and non-DM + non-ISR groups, though the difference was not statistically significant. In addition, the stent diameter (2.75 mm [2.50 mm–3.50 mm]) in the DM + ISR group was significantly smaller than that in the other groups ($P < 0.05$) (Table 2).

Table 2
Comparison of clinical baseline and coronary lesions in the population

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
Age (years)	63.82 ± 9.92	65.17 ± 10.17	64.48 ± 10.22	65.30 ± 9.89	0.722
Male, n (%)	173((73.62%)	49(62.82%)	23(85.19%)	13(65.00%)	0.097
Hypertension, n (%)	173((73.62%)	62(79.49%)	13(48.15%)	17(85.00%)	0.008
Systolic blood pressure mmHg	136.38 ± 21.42	141.29 ± 20.91	129.26 ± 22.18	140.95 ± 17.58	0.055
Diastolic blood pressure, mmHg	79.13 ± 13.17	80.97 ± 13.04	76.74 ± 9.84	78.05 ± 11.60	0.454
Smoking history, n (%)	127(54.04%)	30(38.46%)	18(66.67%)	11(55.00%)	0.037
Hyperlipidemia, n (%)	65(27.66%)	26(33.33%)	7(25.93%)	4(20.00%)	0.625
Follow-up interval (months)	12(1–48)	12(1–37)	13(3–77)	12.5(6–72)	0.022
SAP	110	33	9	11	0.437
ACS	125	44	18	9	
LVEF(%)	61.56 ± 6.62	61.63 ± 7.03	61.04 ± 8.55	59.43 ± 9.62	0.692
LA(mm)	34.49 ± 5.10	35.32 ± 4.58	34.35 ± 5.25	34.19 ± 4.72	0.696
Bracket diameter (mm)	3.00(2.25–4.00)	3.00(2.25–4.00)	3.00(1.50–4.00)	2.75(2.50–3.50)	0.026
Bracket length (mm)	24.00(12.00–38.00)	24.00(12.00–38.00)	29.00(12.00–36.00)	24.00(12.00–38.00)	0.121
Maximum balloon inflation pressure, atm	14.00(8.00–20.00)	17.00(9.00–20.00)	16.00(8.00–20.00)	16.00(12.00–20.00)	0.540
Average balloon inflation pressure, atm	15.00(4.00–26.00)	16.00(9.00–22.00)	15.00(8.00–19.00)	16.00(10.00–20.00)	0.571
Data were expressed as mean ± SD, median with minimum and maximum or n (%)					

Re-examination of laboratory parameters of pre-PCI and repeat CAG

Table 3 shows that the levels of TC, TG, HDL-c, LDL-c, ApoB100, ApoE, RPL-c, non-HDL-c, TC / HDL-c, TG / HDL-c in the four groups are equivalent pre-PCI and repeat CAG. However, the ApoA1 level in the DM + non-ISR and DM + ISR groups was lower than that in the respective non-DM + non-ISR and non-DM + ISR groups for pre-PCI and repeat CAG. There were statistical differences pre-PCI (1.00 ± 0.24 vs 1.09 ± 0.30 , $P < 0.05$; 1.01 ± 0.21 vs 1.22 ± 0.52 , in the DM + non-ISR and DM + ISR groups vs the non-DM + non-ISR and non-DM + ISR groups, respectively $P < 0.05$). The DM + non-ISR and DM + ISR groups exhibited lower levels of ApoA1 / ApoB100 compared to the corresponding non-DM + non-ISR and non-DM + ISR groups for pre-PCI and repeat CAG. These differences between the DM-ISR group and the non-DM + ISR group were significant ($P < 0.05$) (pre-PCI 1.35 ± 0.32 vs 1.76 ± 0.86 , $P < 0.05$, repeat CAG 1.62 ± 0.53 vs 2.17 ± 1.34 , $P < 0.05$). The DM + non-ISR and the DM + ISR groups had a higher level of HbA1c, which reflected the blood glucose control level, compared to the corresponding non-DM + non-ISR and non-DM + ISR groups ($P < 0.05$), of which the DM + ISR group demonstrated the highest level; this difference was significant compared with DM + non-ISR group ($P < 0.05$) (pre-PCI 8.15 ± 1.48 vs 7.65 ± 1.66 , $P < 0.05$; repeat CAG 8.12 ± 1.84 vs 7.49 ± 1.38 , $P < 0.05$) (Table 3).

Table 3
Comparison of the laboratory parameters for the four groups

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
Pre-PCI					
TC,mmol/L	4.22 ± 1.03	4.07 ± 1.51	3.99 ± 1.11	3.95 ± 0.83	0.512
TG,mmol/L	1.57 ± 1.01	1.57 ± 0.79	1.82 ± 1.55	1.46 ± 0.99	0.661
HDL-c,mmol/L	1.10 ± 0.32	1.00 ± 0.27	1.10 ± 0.52	1.08 ± 0.28	0.119
LDL-c,mmol/L	2.50 ± 0.79	2.41 ± 1.04	2.18 ± 0.92	2.39 ± 0.82	0.316
ApoA1,g/L	1.09 ± 0.30	1.00 ± 0.24*	1.22 ± 0.52	1.01 ± 0.21 [#]	0.015
ApoB100,g/L	0.81 ± 0.20	0.81 ± 0.25	0.74 ± 0.25	0.80 ± 0.21	0.511
ApoE,mg/L	43.08 ± 17.50	40.76 ± 16.14	37.86 ± 15.49	37.08 ± 12.34	0.254
TC/HDL-c	4.10 ± 1.49	4.27 ± 1.65	3.98 ± 1.24	3.83 ± 1.15	0.612
TG/HDL-c	1.22(0.26-9.70)	1.42(0.38-6.39)	1.35(0.51-5.52)	1.09(0.44-6.51)	0.256
LDL-c/HDL-c	2.44 ± 0.99	2.55 ± 1.16	2.20 ± 0.94	2.44 ± 1.03	0.473
ApoA1/ ApoB100	1.43 ± 0.54	1.34 ± 0.54	1.76 ± 0.86	1.35 ± 0.32 [#]	0.028
RPL-c,mmol/L	0.69 ± 0.47	0.66 ± 0.39	0.72 ± 0.47	0.61 ± 0.40	0.803
Non-HDL-c,mmol/L	3.12 ± 1.01	3.07 ± 1.48	2.90 ± 0.96	2.86 ± 0.79	0.640
Hcy,μmol/L	19.06(2.80-74.37)	15.39(6.01-94.00)	21.95(9.28-35.06)	14.07(6.67-110.70)	0.195
HbA1c,%	5.90 ± 0.83	7.65 ± 1.66*	5.76 ± 1.77	8.15 ± 1.48 ^{#&}	0.000
UC,μmol/L	356.65 ± 101.45	314.39 ± 97.09*	328.91 ± 77.90	295.45 ± 102.78	0.001
Repeat CAG					
TC,mmol/L	3.34 ± 0.88	3.21 ± 0.88	3.24 ± 0.79	2.99 ± 0.69	0.512
TG,mmol/L	1.38 ± 0.90	1.42 ± 0.65	1.30 ± 0.88	1.25 ± 0.65	0.856
HDL-c,mmol/L	1.06 ± 0.36	0.97 ± 0.28	1.06 ± 0.34	0.97 ± 0.29	0.244
LDL-c,mmol/L	1.66 ± 0.57	1.61 ± 0.58	1.52 ± 0.53	1.47 ± 0.46	0.382
ApoA1,g/L	1.10 ± 0.31	1.04 ± 0.29	1.19 ± 0.55	0.95 ± 0.25	0.058
ApoB100,g/L	0.62 ± 0.16	0.63 ± 0.17	0.64 ± 0.25	0.62 ± 0.16	0.954
ApoE,mg/L	32.78 ± 14.92	31.00 ± 14.09	29.82 ± 10.64	31.74 ± 13.76	0.686
TC/HDL-c	3.36 ± 1.21	3.47 ± 1.11	3.22 ± 0.99	3.24 ± 0.83	0.747
TG/HDL-c	1.12(0.20-17.38)	1.36(0.21-5.28)	1.00(0.25-4.58)	1.13(0.55-4.02)	0.086
LDL-c/HDL-c	1.69 ± 0.73	1.75 ± 0.69	1.55 ± 0.70	1.69 ± 0.71	0.660
ApoA1/ ApoB100	1.86 ± 0.64	1.74 ± 0.57	2.17 ± 1.34	1.62 ± 0.53 [#]	0.033
RPL-c,mmol/L	0.66 ± 0.43	0.71 ± 0.45	0.66 ± 0.37	0.55 ± 0.23	0.489
Non-HDL-c,mmol/L	2.28 ± 0.83	2.24 ± 0.82	2.18 ± 0.77	2.02 ± 0.58	0.569
Hcy,μmol/L	13.25(3.50-63.04)	12.35(5.58-40.80)	10.06(6.76-57.87)	13.81(7.21-33.20)	0.158
HbA1c,%	5.96 ± 0.73	7.49 ± 1.38*	6.01 ± 0.65	8.12 ± 1.84 ^{#&}	0.000
UC,μmol/L	363.04 ± 97.87	334.47 ± 96.36	337.35 ± 85.45	337.93 ± 95.72	0.105
Data were expressed as mean ± SD, median with minimum and maximum					

All four groups showed a decrease in the levels of TC, TG, LDL-c, ApoB100, and ApoE level at repeat CAG compared with pre-PCI, which indicated that conventional statin drug therapy after PCI exhibited a certain effect, but that HDL-c and ApoA1 prohibited the difference in performance. The HDL-c level in the DM + ISR group showed a significant downward trend, while the other three groups maintained the pre-PCI level. At repeat CAG, the ApoA1 level in the DM + ISR group was lower than that pre-PCI, while the other three groups had higher levels of ApoA1 than at pre-PCI. The HbA1c level in the non-DM + ISR group showed a significant increase, while in the other three groups it remained unchanged, suggesting that there may be patients with an abnormal glucose tolerance in the non-DM + ISR group. The uric acid level in the DM + ISR group showed a remarkably increased trend, which was significantly larger than the other three groups, but it did not reach statistical significance (Table 4).

Table 4
Comparison of the changes of laboratory parameters between the four groups at pre-PCI and repeat CAG

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
△TC,%	-18.72 ± 21.11	-15.51 ± 32.62	-16.89 ± 22.00	-22.84 ± 21.69	0.628
△TG,%	-0.56 ± 53.66	-2.41 ± 45.30	-11.53 ± 43.24	3.51 ± 46.61	0.779
△HDL-c,%	0.88 ± 30.69	-0.07 ± 22.69	-0.24 ± 20.00	-10.34 ± 21.08	0.425
△LDL-c,%	-29.84 ± 25.85	-26.24 ± 34.12	-27.63 ± 24.21	-32.98 ± 33.70	0.730
△ApoA1,%	6.96 ± 39.78	8.32 ± 33.29	6.26 ± 59.55	-3.67 ± 27.00	0.694
△ApoB100,%	-20.71 ± 22.57	-18.24 ± 27.37	-10.74 ± 27.02	-15.70 ± 27.54	0.295
△ApoE,%	-17.96 ± 36.55	-19.55 ± 30.10	-11.70 ± 36.19	-7.53 ± 44.04	0.519
△TC/HDL-c,%	-15.40 ± 27.24	-13.13 ± 36.27	-14.11 ± 23.75	-11.96 ± 23.11	0.918
△TG/HDL-c,%	8.22 ± 77.77	2.87 ± 54.09	-10.41 ± 44.40	19.99 ± 57.38	0.526
△LDL-c/HDL-c, %	-26.28 ± 32.22	-23.16 ± 42.39	-22.58 ± 36.22	-22.60 ± 39.79	0.730
△ApoA1/ ApoB100,%	44.66 ± 66.02	45.58 ± 60.43	37.25 ± 102.55	28.28 ± 56.09	0.734
△RPL-c,mmol/L	-0.03 ± 0.39	-0.06 ± 0.52	-0.03 ± 0.48	-0.03 ± 0.47	0.572
△Non-HDL-c, mmol/L	-0.86 ± 0.92	-0.90 ± 1.56	-0.75 ± 0.98	-0.88 ± 0.95	0.960
△Hcy,μmol/L	-4.10 ± 012.58	-3.76 ± 13.82	-5.93 ± 15.69	-7.07 ± 24.08	0.859
△HbA1c,%	0.03 ± 0.56	-0.20 ± 1.88	0.42 ± 1.84	-0.13 ± 1.51	0.382
△UC,μmol/L	10.55 ± 82.34	16.80 ± 62.85	-0.17 ± 56.27	41.11 ± 99.94	0.191
Data were expressed as mean ± SD					
Note: TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB100, apolipoprotein B100; ApoE, contained Lipoprotein E; RPL-C, residual lipoprotein; Non-HDL-c, non-high-density lipoprotein cholesterol; Hcy, homocysteine; HbA1c, glycated haemoglobin A1c; UC, uric acid.					

We further compared the changes of blood lipid composition of the DM + non-ISR and the DM + ISR groups for the pre-PCI and repeat CAG at follow-up. The TC, LDL-c, ApoB100, ApoE, non-HDL-c, TC / HDL-c, LDL-c / HDL-c levels showed a downward trend, and for both groups, the above indicators were statistically different at pre-PCI and repeat CAG ($P < 0.05$). The decline in the levels of TG and TG / HDL-c in the DM + non-ISR group was greater than those of the DM + ISR group. The HDL-c and ApoA1 levels in the DM + ISR group showed a downward trend, while in the DM + non-ISR group these two indicators remained unchanged or were slightly increased. Similarly, the increase in the levels of ApoA1 / ApoB100 in the DM + non-ISR group was greater than those in the DM + ISR group (Fig. 1,2).

Gensini Points And Progress

Table 5 reveals that in the DM + ISR and DM + non-ISR groups, the Gensini score and the detaching stent Gensini score (no-stent) at the time of PCI and repeat CAG were higher than those of the non-DM + non-ISR and Non-DM + ISR groups ($P < 0.05$). Regarding the Gensini

progress, the DM + ISR and DM + non-ISR groups showed more progress compared with the non-DM groups, but did not reach statistical significance.

Table 5
Four PCI groups and a review of the CAG Gensini score and progress

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
PCI					
Gensini score	48.50(8.00~196.00)	54.00(10.00~150.00)	38.00(4.00~136.00)	52.00(13.00~96.00)	0.082
Ln(Gensini)	3.81 ± 0.64	4.01 ± 0.61*	3.63 ± 0.89	3.87 ± 0.57	0.040
Gensini (no-stent)	12.00(0.00~80.00)	19.00(0.00~133.00)	10.00(0.00~56.00)	24.00(0.00~53.00)	0.015
LnGensini (non-stent)	2.62 ± 0.95	2.84 ± 0.99	2.52 ± 1.04	3.00 ± 0.71	0.133
Repeat CAG					
Gensini (no-stent)	13.00(0.00~85.00)	21.00(0.00~140.00)	10.00(0.00~68.00)	25.50(0.00~74.00)	0.002
LnGensini (non-stent)	2.68 ± 0.95	2.90 ± 1.06	2.45 ± 1.00	3.07 ± 0.67	0.069
△Gensini (no-stent)	1.32 ± 17.00	4.42 ± 21.44	0.91 ± 14.82	2.90 ± 14.28	0.598
Data were expressed as mean ± SD, median with minimum and maximum					
Note: Compared with non-DM + non-ISR * P < 0.05					

Changes of the inflammation index for all patients at pre-PCI and later repeat CAG

Table 6 shows that there are no significant differences in CRP, WBC, L, M, Hb, PLT, PDW, RDW, PLT / L, and M / HDL-c in the four groups pre-PCI. However, at repeat CAG, the CRP, WBC, and N levels in the DM + non-ISR and DM + ISR groups were higher than those in the corresponding non-DM + non-ISR and non-DM + ISR groups. Considering the above three indexes, the DM + ISR group had the highest values compared with the other three groups (P < 0.05). Further exploration of the changes in the inflammation index revealed that the DM + ISR group prohibited an increasing trend in the WBC and N values(WBC, pre-PCI 6.86 ± 2.37,repeat CAG 7.07 ± 2.63;N, pre-PCI 4.55 ± 2.05,repeat CAG 4.93 ± 2.50) while the other three groups showed a downward trend. There were statistical differences between the DM + ISR and the DM + non-ISR groups (△ WBC 0.20 ± 1.78 vs 1.91 ± 3.25, P < 0.05; △ N 0.41 ± 1.54 vs 1.84 ± 3.28, P < 0.05) (Table 7). Figure 3 shows more intuitively that the levels of WBC, N, N / L, and CRP in the DM + ISR group present an increasing trend at repeat CAG compared to pre-PCI. However, the levels of WBC, N, N / L, and CRP in the DM + non-ISR group decreased significantly, and there was a statistically significant difference between the index at pre-PCI and at repeat CAG (P < 0.05). (Fig. 3a-d).

Table 6
Inflammation indexes in the four groups at pre-PCI and repeat CAG

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
Pre-PCI					
CRP,mg/L	1.64(0.00-110.13)	2.03(0.50-100.87)	2.11(0.00-22.00)	3.15(0.00-32.18)	0.573
WBC,10 ⁹ /L	7.66 ± 3.28	8.02 ± 3.67	6.37 ± 2.52	6.86 ± 2.37	0.109
L, 10 ⁹ /L	1.50 ± 0.59	1.62 ± 0.75	1.35 ± 0.51	1.73 ± 0.90	0.109
N, 10 ⁹ /L	5.65 ± 3.38	5.86 ± 3.37	4.46 ± 2.38	4.55 ± 2.05	0.121
M, 10 ⁹ /L	0.46 ± 0.26	0.48 ± 0.40	0.44 ± 0.23	0.45 ± 0.19	0.940
Hb,g/L	134.65 ± 17.37	133.42 ± 15.78	133.37 ± 15.44	135.05 ± 22.63	0.938
PLT, 10 ⁹ /L	190.26 ± 59.20	175.73 ± 49.36	170.00 ± 43.57	181.60 ± 55.94	0.099
RDW,%	13.09 ± 0.90	13.47 ± 2.00	13.07 ± 0.63	13.33 ± 0.78	0.103
PDW,%	15.16 ± 2.72	15.58 ± 2.38	16.23 ± 2.94	15.12 ± 2.26	0.180
N/L	3.17(0.76-28.14)	2.93(1.10-27.64)	3.13(0.76-11.01)	2.79(0.92-13.50)	0.509
PLT/L	144.60 ± 73.44	128.24 ± 63.28	138.54 ± 51.02	133.06 ± 79.75	0.334
M/HDL-c	0.46 ± 0.32	0.52 ± 0.47	0.45 ± 0.26	0.45 ± 0.22	0.592
Repeat CAG					
CRP,mg/L	0.75(0.50-186.00)	0.97(0.50-42.95)	1.37(0.50-70.80)	2.33(0.50-48.02)	0.009
WBC,10 ⁹ /L	5.86 ± 1.50	6.21 ± 1.69	5.60 ± 2.01	7.07 ± 2.63 ^{*#&}	0.008
L, 10 ⁹ /L	1.52 ± 0.73	1.48 ± 0.56	1.32 ± 0.43	1.32 ± 0.43	0.572
N, 10 ⁹ /L	3.79 ± 1.21	4.14 ± 1.33	3.69 ± 1.71	4.93 ± 2.50 ^{*#&}	0.002
M, 10 ⁹ /L	0.42 ± 0.17	0.41 ± 0.20	0.43 ± 0.18	0.46 ± 0.20	0.756
Hb,g/L	136.35 ± 16.89	132.96 ± 15.46	133.48 ± 15.46	130.79 ± 18.75	0.266
PLT, 10 ⁹ /L	175.90 ± 55.64	163.37 ± 51.74	160.68 ± 55.74	189.58 ± 55.89	0.121
RDW,%	13.26 ± 0.90	13.51 ± 1.00	13.42 ± 1.07	13.33 ± 1.18	0.262
PDW,%	13.26 ± 0.90	13.51 ± 1.00	13.42 ± 1.07	13.33 ± 1.18	0.262
N/L	2.58(0.71-16.00)	2.86(1.07-8.63)	2.56(1.40-7.62)	3.17(1.53-11.84)	0.175
PLT/L	128.89 ± 54.08	122.19 ± 49.84	131.07 ± 56.10	146.67 ± 78.18	0.377
M/HDL-c	0.44 ± 0.23	0.47 ± 0.28	0.43 ± 0.19	0.55 ± 0.33	0.311
Data were expressed as mean ± SD, median with minimum and maximum					

Table 7
The changes of inflammation indicators in the four groups between pre-PCI and re-examination of CAG

	Non-DM + non-ISR	DM + non-ISR	Non-DM + ISR	DM + ISR	P
△CRP,mg/L	-3.97 ± 22.13	-3.93 ± 16.79	0.38 ± 12.11	1.14 ± 13.60	0.564
△WBC,10 ⁹ /L	-1.76 ± 2.80	-1.91 ± 3.25	-0.83 ± 2.41	0.20 ± 1.78* [#]	0.013
△L, 10 ⁹ /L	-0.02 ± 0.66	-0.13 ± 0.58	0.02 ± 0.49	-0.23 ± 0.92	0.178
△N, 10 ⁹ /L	-1.85 ± 3.06	-1.84 ± 3.28	-0.85 ± 2.58	0.41 ± 1.54* [#]	0.009
△M, 10 ⁹ /L	-0.04 ± 0.26	-0.07 ± 0.33	-0.02 ± 0.23	0.00 ± 0.23	0.653
△Hb,g/L	1.14 ± 19.76	-0.11 ± 14.21	-0.08 ± 11.97	-1.95 ± 14.93	0.867
△PLT, 10 ⁹ /L	-14.86 ± 44.50	-12.95 ± 35.55	-11.12 ± 38.19	-5.05 ± 43.96	0.270
△RDW	0.18 ± 1.01	0.02 ± 2.14	0.38 ± 0.99	-0.02 ± 0.86	0.611
△PDW	1.11 ± 3.65	0.74 ± 2.55	0.27 ± 3.00	0.34 ± 2.59	0.492
△N/L	-1.82 ± 4.55	-1.58 ± 4.35	-0.67 ± 2.73	0.29 ± 1.79	0.149
△PLT/L	-14.84 ± 74.90	-7.72 ± 58.75	-9.11 ± 59.00	11.02 ± 53.17	0.436
△M/HDL-c	-0.03 ± 0.31	-0.07 ± 0.39	-0.01 ± 0.29	0.09 ± 0.30	0.298
Data were expressed as mean ± SD					
Note: CRP, C-reactive protein; WBC, white blood cells; L, lymphocytes; M, monocytes; Hg, haemoglobin; PLT, platelet values; PDW, platelet width; RDW, red blood cell width; PLT / N, platelets / lymphocytes Ratio; M / HDL-c monocytes / high-density lipoprotein cholesterol. Compared with non-DM + non-ISR * P < 0.05, compared with non-DM + ISR [#] P < 0.05, compared with DM + non-ISR comparison ^{&} P < 0.05.					

Correlation of risk factors with the changes of the coronary Gensini score in DM

The Gensini score (no-stent) was calculated for the DM + non-ISR and DM + ISR groups at pre-PCI period and repeat CAG, and correlation analysis was used to evaluate the risk factors and the Gensini score change. We found that levels of TG / HDL-c at the pre-PCI period and TG, WBC, N level, LDL-c / HDL-c, N / L, TG / HDL-c at the repeat CAG period were positively correlated with the △Gensini, with correlation coefficients of 0.210, 0.239, 0.229, 0.315, 0.314, 0.327, and 0.349, respectively. Furthermore, △Gensini was negatively correlated with HDL-c, and ApoA1 levels at the pre-PCI period, and the HDL-c level at the repeat CAG period, with correlation coefficients of -0.233, -0.227, and -0.301, respectively (Fig. 4 a-j).

Analysis of multiple risk factors of DM-ISR with the cumulative incidence of ISR Kaplan-Meier plot in the DM and non-DM groups

Binary logistics regression analysis was used to analyse the risk factors of ISR in patients with DM. Single factor logistics regression analysis showed that △WBC and △N were identified as risk factors (△WBC, OR 1.466, 95% CI 1.079–1.993; △N OR 1.612, 95% CI 1.125–2.310), but in the multivariate regression analysis model, △N and HbA1c-B were revealed as risk factors, (△N, OR 1.929, 95% CI 1.216–3.058; HbA1c-B OR 1.559, 95% CI 1.001–1.707) (Table 8). According to ROC, the cut-off values were: △N: $-0.43 \times 10^9 / L$; △WBC: $-0.565 \times 10^9 / L$; HbA1c-B 7.75%. Based on the independent predictive factors screened from the logistic regression analysis, we incorporated these factors into the restenosis risk prediction model ($P = [\exp (-4.842 + 0.562 (\Delta N) + 0.473 (HbA1c-B))] / [1 + \exp (-4.842 + 0.562 (\Delta N) + 0.473 (HbA1c-B))]$), to test whether this model was able to predict DES-ISR risk. We used the ROC curve to confirm that △N, △WBC, HbA1c-B, and this model were predictive of DES-ISR, then we observed that the restenosis risk prediction model presented a highly predictive value for raised restenosis risk (△N, AUC 0.735, 95% CI 0.603–0.858; △WBC, AUC 0.682, 95% CI 0.535–0.828; HbA1c-B, AUC 0.609, 95% CI 0.453–0.765); and for the restenosis risk prediction model for restenosis risk, AUC 0.808, 95% CI 0.705–0.912 (Fig. 5a). The cumulative incidence of ISR in the DM group was 20.41%, which was higher than that in the non-diabetic group at 10.31%, (HR 2.369 [95% CI (1.231–4.557)]) (Fig. 5b).

Table 8
Univariate and multivariate logistic regression analysis of predictors of stent restenosis in diabetic patients

Univariable Analysis			Multivariable Analysis	
Variables	OR(95%CI)	P	OR(95%CI)	P
ApoA1-B/ApoB100-B	1.008(0.368–2.755)	0.998		
ApoA1-F/ApoB100-F	0.998(0.993–1.003)	0.410		
HbA1c-B	1.196(0.871–1.633)	0.258	1.559(1.001-2.428)	0.050
HbA1c-F	1.287(0.930–1.780)	0.129		
WBC-F	1.233(0.960–1.584)	0.101		
N-F	1.293(0.964–1.735)	0.086		
△WBC	1.466(1.079–1.993)	0.014		
△N	1.612(1.125–2.310)	0.009	1.929(1.216–3.058)	0.005
Note: ApoA1, apolipoprotein A1; ApoB100, apolipoprotein B100; HbA1c, glycated haemoglobin A1c; WBC, white blood cells; N, neutrophils; B, pre-PCI period; F, repeat coronary angiography period.				

Relationship between LDL-c control level and Gensini score progress in patients with DM

According to whether the LDL-c value was less than 1.8 mmol/L at repeat CAG or was decreased by more than 50% compared with pre-PCI, all patients were assigned to the LDL-c achieved group or the LDL-c failure group. The coronary artery Gensini scores of the two groups (DM + non-ISR, and DM + ISR) at the pre-PCI period were similar, with no statistical difference (LDL-c achieved group 60.86 ± 35.11 ; LDL-c failure group 68.59 ± 34.82) (Fig. 6a). then the Gensini score (no-stent) was calculated for both groups at pre-PCI and at repeat CAG, respectively. The LDL-c failure group showed a remarkable increase in the Gensini score (no-stent) [pre-PCI, 20 (6-144); repeat CG, 27 (2-140), $P < 0.05$]. The Δ Gensini score for the LDL-c achieved group was significantly reduced compared to the LDL-c failure group, (Δ Gensini score, LDL-c achieved group, 0.56 ± 12.08 ; LDL-c failure group, 11.87 ± 31.18 , $P < 0.05$) (Fig. 6b, c).

Discussion

Our study revealed that patients with DM were susceptible to an occurrence of ISR. The reduction of HDL-c and ApoA1 levels, the increase of inflammation indicators (leukocytes and neutrophils) and HbA1c levels were possible risk factors for the occurrence of ISR in patients with DM. The progression of coronary stenosis was more obvious in patients with DM in which the LDL-c level failed to achieve the control target. Our findings indicated that patients with coronary artery disease who also had DM were at a high risk for an occurrence of ISR if they had preoperative risk factors including dyslipidaemia, elevated inflammatory factors, and a high Gensini score. Our results also showed that dynamic observation of the changes of preoperative and postoperative comprehensive risk factors was helpful to identify ISR in patients with DM.

Patients with DM are 2–4 times more likely to suffer from cardiovascular disease than patients without DM[7]. Additionally, cardiovascular disease accounts for 3/4 of the causes of death in patients with DM. Notably, DM itself can lead to a greater inflammatory response, and a more diffuse and rapid progression of atherosclerosis [7]. The ISR occurrence rate in patients with DM is 10% higher than that in patients without DM [14–16]. Our study found that ISR accounted for 20/98 vs 27/262 in DM and non-DM populations respectively ($P < 0.05$), which was consistent with previous studies.

DM inhibits the ability of vascular endothelial cells to secrete vasodilators such as prostaglandin I_2 (PGI_2) and nitric oxide (NO), while the secretion of vasoconstrictor endothelin-1 increases, which causes vasodilation disorders and vascular sclerosis [8]. In addition, insulin can directly promote the release of platelet-derived NO, activate platelet-derived cyclic guanosine monophosphate, and inhibit platelet aggregation. In addition, platelet aggregation is regulated by endothelial-derived PGI_2 and NO, As a result, DM could reduce the secretion of endothelial-derived PGI_2 and NO, which are secreted by the vascular endothelium, to ultimately induce platelet aggregation.

Hyperglycaemia causes increased synthesis of thromboxane A_2 , which further leads to vasoconstriction and platelet aggregation [17]. Also, due to the activation of partial coagulation factors F_I and F_{II} , tissue factors, and Von Willibrand factors, patients with DM are in a hypercoagulable state, in which they are prone to form thrombosis, which can lead to ischaemia [8].

In addition, multiple cross-sectional studies have shown that the levels of inflammatory factors such as CRP, interleukin-6, and tumour necrosis factor- α in patients with DM or in patients with insulin resistance are higher than those in the control group [18], and drugs such as rosiglitazone and pioglitazone can reduce CRP levels [19]. DM could also increase vascular extracellular matrix degradation-related enzyme (matrix metalloprotease-2, matrix metalloprotease-9) levels, resulting in vascular remodelling [20]. Consequently, the majority of the vascular lesions caused by DM are diffuse, and the lack of compensation for the blood vessels leads to a high incidence of cardiovascular events. Therefore, DM can result in vascular lesions arising from multiple mechanisms such as vasodilation disorder, platelet accumulation, thrombosis, inflammation, vascular remodelling, among others. Intensive blood glucose control can reduce the occurrence of cardiovascular events in type 1 DM, but no significant benefit was obtained in people with type 2 DM with an HbA1c level $\leq$ 7.0% [21, 22]. Further research found that in the BMS implanted population, HbA1c levels were negatively correlated with BMS-ISR, but were not significantly correlated with DES-ISR [23]. This finding is inconsistent with our results.

Approximately 67% of patients with DM have dyslipidaemia, most of whom have an abnormally elevated level of VLDL-c and triglycerides and a low HDL-c level, while the level of LDL-c is mostly normal [24]. In patients with DM with an VLDL-c $\geq$ 0.52 mmol / L, the HR of the VLDL-c and ISR reaches 3.01; thus, the VLDL-c can be used as an independent risk factor for ISR. The mechanism is that DM is complicated by insulin resistance, which causes an excessive production of VLDL-c in the liver, which decreases the ability to remove lipids from the blood after meals. Also, each VLDL-c can transfer more cholesterol than LDL-c; consequently, VLDL-c is engulfed by vascular wall macrophages, which induces inflammation and atherosclerosis, and the resulting continuous inflammatory stimulation and cell proliferation eventually lead to DM-ISR [25, 26]. Our study found that at the pre-PCI and repeat CAG periods the values of CAG TC, TG, HDL-c, LDL-c, ApoB100, ApoE, RPL-c, non-HDL-c, TC/HDL-c, and TG / HDL-c in the DM non-ISR and DM + ISR groups were roughly equivalent, and revealed no statistical differences. However, the levels of ApoA1 in the DM + non-ISR and in the DM + ISR groups were lower than those in the non-DM + non-ISR and non-DM + ISR groups at the pre-PCI and repeat CAG periods. The DM + ISR group had the highest level of HbA1c and the most significant coronary stenosis Gensini score progression, indicating that this group had the worst blood glucose control, indirectly demonstrated that the level of blood glucose control in DM can significantly influence the progression of disease and the occurrence of ISR. In addition, the changes of the inflammation indicators such as WBCs and neutrophils in the DM + ISR group were the most obvious, suggesting that the inflammatory response was involved in the process of DM-related ISR. Multivariate regression analysis also concluded that the glycated haemoglobin and neutrophil change values were independent risk factors for ISR.

This study includes some limitations. This study did not employ randomisation; therefore, there was a possibility for selection bias. Also this study was conducted as a single centre with DES implantation patients. A future study with an increased number of patients is required to observe whether there are statistical differences. This study could only identify the association between clinical risk factors and restenosis, it could not confirm a causal relationship. The ISR definition used in this study was based on the independent evaluation of CAG images by two interventional cardiologists. Our study did not use intravascular ultrasound or optical computed tomography to assess the degree of in-stent re-narrowing. Most of the previous relevant studies have focused on predicting ISR through the pre-PCI baseline risk factor level.

Despite these limitations, our study focused on the comprehensive study of ISR in patients with DM with regard to blood lipid, blood glucose and inflammation control levels, which has not been extensively studied.

Conclusions

In conclusion, this study focus on the dynamic change of lipid and inflammatory indexes, rarely in previous researches. We concluded that coronary artery disease patients with DM had a high risk for ISR if they had preoperative risk factors including dyslipidaemia, elevated inflammatory factors, and a high Gensini score. Dynamic observation of the changes of the preoperative and postoperative comprehensive risk factors is helpful to identify ISR in patients with DM.

Abbreviations

ApoA1: Apolipoprotein

ApoB100: Apolipoprotein B100

ApoE: Apolipoprotein E

AUC: Area under the curve

BMS: Bare metal stents

CAG: coronary angiography

Ccr: creatinine

CHD: Coronary heart disease

CRP, C-reactive protein

DES: Drug-eluting stent

DM, Diabetes Mellitus

Hb: Haemoglobin

HbA1c: Glycated haemoglobin

Hcy: Homocysteine

HDL-c: High-density lipoprotein cholesterol

HR: Hazard ratio

ISR: In-stent restenosis

IVUS: intravascular ultrasonography

L: Lymphocyte

LA: Left atrium

LDL-c: Low-density lipoprotein

LVEF: left ventricular ejection

M: Monocytes

MI: Myocardial infarction

N: Neutrophil

NO: Nitric oxide

PCI: Percutaneous coronary intervention

PDW: Platelet distribution width

PGI2: Prostaglandin I2

PLT: platelet value

RBC: Red blood cell

RDW: RBC distribution width

ROC: Receiver operating characteristic curve

RPL-C: Residual lipoprotein

TC: Total cholesterol

TG: Triglyceride

TIMI: thrombolysis in myocardial infarction

TLR: Target lesion revascularisation

UC: Uric acid

WBC: White blood cell

Declarations

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Authors' contributions

Z-SG and H-BJ completed the project, analyzed the data, and drafted the manuscript. H-BJ designed the study, interpreted the data and contributed to critically revising the manuscript. J-LQ interpreted the data and contributed to revising the manuscript. X-JJ, C-ZL, T-AQ, J-L, H-JB, Z-B, Z-ZX, S-FJ, Z-XY, Z-R, J-FF contributed to recruitment of patients and clinical diagnosis of disease. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Because this was a prospective study, all subjects were required to sign an informed consent form. The study complied with the Declaration of Helsinki and was approved by the ethics committee of the second affiliated hospital of Jiaxing University (no. 20181102H02).

Consent for publication: Not applicable

Competing interests

We declare that we have no conflict of interest.

Authors' details

1 Department of Cardiology, The Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang Province, China

2 Medical College, Jiaxing University, Jiaxing, Zhejiang Province, China

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Figures

Figure 1

Comparison of blood lipid profile changes between two groups before PCI and before re-examination. Note: TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ApoA1, Apolipoprotein A1; ApoB100, apolipoprotein B100; ApoE, apolipoprotein E; Non-HDL-c, non-high-density lipoprotein cholesterol. Baseline, pre-PCI; Follow-up, repeat CAG. * P < 0.05.

Figure 2

Comparison of blood apolipoprotein changes between the two groups before PCI and before re-examination. Note: ApoA1 , Apolipoprotein A1; ApoB100, apolipoprotein B100; ApoE, apolipoprotein E; * $P < 0.05$.

Figure 3

Comparison of inflammation indexes between the two groups before PCI and before re-examination. Note: CRP, C-reactive protein; WBC, white blood cells; N, neutrophils; L, lymphocytes. * $P < 0.05$. Baseline, pre-PCI; Follow-up, repeat CAG.

Figure 4

Linear correlation analysis of risk factors and Δ Gensini Note: TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; LDL-c, low-density lipoprotein cholesterol; N, neutrophils; L, lymphocytes. B: Before PCI; F, before reviewing coronary angiography.

a

b

Figure 5

a. Predictive values of various factors for restenosis risk by ROC curve analysis. Predictive values of Δ N, Δ WBC, HbA1c-B and restenosis risk prediction model for restenosis risk, which were evaluated by ROC. HbA1c, glycated haemoglobin A1c; WBC, white blood cells; N, neutrophils; B, pre-PCI period; restenosis risk prediction model. $P = [\exp (-4.842 + 0.562 (\Delta N) + 0.473 (\text{HbA1c-B}))] / [1 + \exp (-4.842 + 0.562 (\Delta N) + 0.473 (\text{HbA1c-B}))]$; b. Kaplan-Meier plot of cumulative incidence of ISR in diabetic and non-diabetic groups.

Figure 6

Relationship between LDL-c control status and Gensini progression. A: Comparison of the baseline of Gensini scores at pre-PCI period between LDL-c achieved group and LDL-c failure group; B: Comparison of difference in Gensini scores(no-stent) change between LDL-c achieved group and LDL-c failure group; C: LDL-c Trend graph of Gensini scores(no-stent) of both LDL-c achieved group and LDL-c failure group. Baseline: pre-PCI; Follow-up: Repeat coronary angiography. *P<0.05.

Supplementary Files

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