New predictors of in-stent restenosis in patients with diabetes mellitus undergoing percutaneous coronary intervention with drug-eluting stent

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Abstract

Background Percutaneous coronary intervention (PCI) had become the major therapeutic procedure for coronary artery disease (CAD), but the high rate of in-stent restenosis (ISR) still remained an unsolved clinical problem in clinical practice. Increasing evidences suggested that diabetes mellitus (DM) was a major risk factor for ISR, but the risk predictors of ISR in CAD patients with DM had not been well characterized. The aim of this study was to investigate the clinical and angiographic characteristic predictors significantly associated with the occurrence of ISR in diabetic patients following coronary stenting with drug-eluting stent (DES). Methods A total of 920 patients with diabetes who diagnosed CAD and underwent coronary DES implantation at Beijing Anzhen Hospital in China were consecutively enrolled from January 2012 to December 2012. Of these, 440 patients underwent the second angiography within ≥ 6 months due to the progression of treated target lesions. Finally, 368 of these patients who met the inclusion and exclusion criteria were followed up by angiography after baseline PCI. According to whether ISR was detected at follow-up angiography, patients were divided into the ISR group (n = 74) and the non-ISR group (n = 294). The independent predictors of ISR in patients with DM were explored by multivariate Cox’s proportional hazards regression models. Results A total of 368 patients (260 women and 108 men) with a mean ages of 58.71 ± 10.25 years were finally enrolled in this study. Of these, ISR occurred in 74/368 diabetic patients (20.11%) by follow-up angiography. Univariate analysis showed that most baseline characteristics of the ISR and non-ISR group were similar. Patients in the ISR group had significantly higher serum very low density lipoprotein cholesterol (VLDL-C), triglyceride (TG) and uric acid (UA) levels, more numbers of target vessel lesions, higher prevalence of multi-vessel disease, higher SYNTAX score, higher rate of previous but lower rate of drinking compared with patients in the non-ISR group. The independent predictors of ISR in patients with DM after DES implantation included VLDL-C (HR = 1.85, 95% CI: 1.24–2.77, P = 0.002), UA (per 50 μmol/L increments, HR = 1.19, 95% CI: 1.05–1.34, P = 0.006), SYNTAX score (per 5 increments, HR = 1.34, 95% CI: 1.03–1.74, P = 0.031) and the history of PCI (HR = 3.43, 95% CI: 1.57–7.80, P = 0.003) by the multivariate Cox’s proportional hazards regression analysis. Conclusions The increased serum VLDL-C and UA level, higher SYNTAX score and the history of previous PCI were independent predictors of ISR in patients with DM after coronary DES implantation. It provided new evidence for physicians to take measures to lower the risk of ISR for the better management of diabetic patients after PCI.

Keywords: Diabetes mellitus; In-stent restenosis; Uric acid; SYNTAX score; Very low density lipoprotein cholesterol

1 Introduction

Percutaneous coronary intervention (PCI) has been the major therapeutic procedure for coronary artery disease (CAD) for about three decades. However, several large-scale clinical trials had confirmed that even in the drug-eluting stent (DES) era, in-stent restenosis (ISR) occurred in 3% to 20% of patients after coronary stenting implantation, which still remained an unsolved clinical problem in clinical practice. Therefore, exploring the reliable risk factors to predict ISR and defining the subgroups of patients at increased risk for ISR would be of massive utility for patients risk assessment and stratification.

Accumulating evidences suggested that diabetes mellitus (DM) played a pivotal role in ISR development. Diabetic patients appeared to have a 2–4 times higher risk of developing ISR after PCI compared to non-diabetic patients. Patients with DM have more complex coronary lesion anatomy with small and diffusely diseased vessels.
thermore, patients with DM often have hypertriglyceridemia and systemic prothrombotic conditions related to the activation of the platelet aggregation and coagulation systems.\(^{[9,10]}\)

Altogether, these made diabetic patients a challenging subpopulation to give more attention and treatment.

To the best of our knowledge, so far, most previous related studies focus on exploring the risk factor of ISR among general CAD patients.\(^{[11–13]}\) the risk predictors of ISR in CAD patients with DM had not been well characterized. Additionally, China had over 92.4 million diabetic patients (9.7% of the adult population), which ranked at top one with the numbers of DM patients and bore a higher diabetes-related burden than other countries.\(^{[14]}\)

Therefore, the aim of our study was to investigate the clinical and angiographic characteristic predictors for functionally significant in occurrence of ISR in diabetic patients after coronary stenting with DES for further understanding the underlying molecular and cellular mechanisms of ISR. This study will provide new evidence for better treatment and prevention of ISR in CAD patients with DM.

2 Methods

2.1 Study patients

A total of 920 patients with diabetes who diagnosed CAD and underwent coronary DES implantation at Beijing Anzhen Hospital (Beijing, China) were consecutively enrolled from January 2012 to December 2012. The inclusion criteria were post PCI patients who had undergone follow-up angiography within ≥ 6 months. Of 920 patients, 480 patients underwent the second angiography due to the progression of untreated nontarget lesions, remaining 440 patients were further selected from the study if they met the exclusion rules.

A total of 440 patients with diabetes who diagnosed coronary heart disease (CHD) and underwent coronary drug-eluting stent (DES) implantation at Beijing Anzhen Hospital (Beijing, China) were consecutively enrolled from January 2012 to December 2012. The inclusion criteria were post PCI patients who had undergone follow-up angiography within ≥ 6 months. Patients were excluded from the study if they met the exclusion rules: (1) patients who died in-hospital after baseline PCI \((n = 8)\); (2) patients with myocardial infarction (MI) within one month of baseline PCI (to exclude potential subacute stent thrombosis of the intervened arterial segment) \((n = 12)\); (3) patients without sufficient clinical and angiographic data at baseline and follow up \((n = 52)\). During the study period, 368 of these patients who met the inclusion and exclusion criteria were followed up by angiography after baseline PCI. Of these, 74 patients with 126 lesions were treated with repeat DES (re-DES) implantation after the occurrence of ISR in the target vessels.

This study was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, and all patients provided written informed consent for participation in this study.

2.2 Stent implantation

All patients received DES implantation in our catheterization center. Stent implantation was performed according to current practice guidelines, and stents were selected by experienced interventional cardiologists. During the procedure, patients received a bolus of 100 IU/kg heparin, with a repeated bolus of 2000 IU heparin to maintain the activated clotting time of ≥ 300 s. All patients received aspirin (100 mg/day was administered) and clopidogrel (300 mg loading dose, followed by 75 mg/day for at least 12 months). When ISR was diagnosed, patients were treated with re-DES implantation. Procedural success was defined as reduction of stenosis to less than 10% residual narrowing, thrombolysis in myocardial infarction (TIMI) flow grade III, with improvement in ischemic symptoms, and without major procedure related complications.\(^{[15]}\)

2.3 Data collection

A standard case report form was used to collect patients’ clinical and demographic characteristics including age, sex, smoking, drinking, CAD risk factors, family history, life style, medical history and coronary angiographic information at baseline PCI and follow-up angiography. During a physical examination, anthropometric indices such as weight, height and blood pressure (BP) were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Coronary angiograms data like the minimal stent diameter, average stent length and the percent diameter stenosis were also recorded by two experienced investigators at baseline and follow-up for coronary angiography analysis.

2.4 Laboratory analysis

Venous blood samples were collected after an overnight for testing the lipid profiles, fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP) and uric acid (UA) level using standard laboratory method at baseline PCI and follow-up angiography. The total cholesterol (TC), TG, FBG and UA were determined according to enzymatic methods. The low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels were measured by homogeneous assays (Daiichi, Tokyo, Japan).
Japan). The Non-high density lipoprotein cholesterol (Non-HDL-C) level was calculated by TC minus HDL-C, and very low density lipoprotein cholesterol (VLDL-C) level was calculated as TC minus LDL-C and HDL-C according to the recommendation of lipid guidelines.\cite{16,17}

### 2.5 Disease definitions

The primary end point of the study was the occurrence of ISR. ISR was defined as a diameter stenosis of \(\geq 50\%\) occurring in the segment inside the stent or a \(5\) mm proximal or distal to the stent at follow-up angiography.\cite{18,19} According to whether ISR was detected, patients were classified into two groups: the ISR group and the non-ISR group. Target lesion was considered the most severe narrowing, identified by angiographic appearance with Electrocardiograph (ECG) changes. Multivessel disease (MVD) was defined as a diameter stenosis of \(\geq 50\%\) occurring in two or more vessels.

Diabetes mellitus was defined as either a previous diagnosis of DM treated with diet, oral agents or insulin or a new diagnosis of DM if FBG \(\geq 7.0\) mmol/L on two occasions during hospitalization.\cite{20} Hypertension was defined by systolic blood pressure (SBP) \(\geq 140\) mmHg and/or diastolic blood pressure (DBP) \(\geq 90\) mmHg, and/or the use of antihypertensive treatment in the past two weeks.\cite{21} Low levels of HDL-C were defined as \(< 1.04\) mmol/L.\cite{22} The severity of coronary artery lesions was quantified with Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score, which was calculated using the online calculator for SYNTAX score.\cite{23}

### 2.6 Statistical analysis

Continuous variables were expressed as mean \(\pm\) SD in case of normal distribution and differences between two groups were determined by two-sided \(t\)-test. Data were expressed as medians (interquartile ranges, \(P_{25}, P_{75}\)) in case of skewed distribution and compared between two groups using the Mann-Whitney test. Categorical variables are presented as counts (percentages) and compared by Chi-square test.

Univariate Cox’s proportional hazards regression modeling was performed to identify determinants of ISR in diabetic patients firstly. Baseline variables were selected if they had either a clinically plausible relation with the ISR or appeared to be imbalanced between ISR and non-ISR patients with a \(P\)-value < 0.2. The potential variables were entered into multivariate Cox’s proportional hazards regression modeling using the stepwise method (entry, 0.05; removal, 0.05) to determine their independent risk associated with ISR in diabetes. The variables included traditional risk factors (age, gender, BMI, current smoking, drinking, SBP), lipid profiles (LDL-C, HDL-C, VLDL-C, TG), angiographic factors (minimal stent diameter, average stent length), SYNTAX score, medical history, and other biomarkers (UA, CRP). The hazard ratio (HR) and 95\% confidence intervals (95\% CI) were calculated to estimate the adjusted risk of ISR in diabetic patients. The predictive value of the Cox’s regression model was evaluated using the area under the receiver operating characteristics curve (AUC).

Statistical analyses were performed using SPSS software for Windows (version 20.0, SPSS Inc., Chicago, IL). Two tailed \(P < 0.05\) was considered statistically significant in all analyses.

### 3 Results

A total of 368 patients (260 women and 108 men) with mean ages of 58.71 \(\pm\) 10.25 years were enrolled in this study. Repeat angiography after baseline PCI was conducted with a mean time of 15.85 \(\pm\) 9.18 months follow-up. Angiography result showed that ISR occurred in 74/368 diabetic patients (20.11\%). According to whether ISR was detected, patients were divided into an ISR group (\(n = 74\)) and Non-ISR group (\(n = 294\)).

#### 3.1 Baseline clinical characteristics

The baseline clinical characteristics were displayed in Table 1. No significant differences were found between the ISR and Non-ISR group in terms of age, gender, BMI, smoking, history of hypertension, myocardial infarction (MI), stroke, and the family history of CAD. Patients with ISR had lower drinking rates (2.7\% \(vs\) 17.0\%, \(P = 0.026\)), whereas the percentage of patients with prior PCI was higher in the ISR group than that in the Non-ISR group (24.3\% \(vs\) 8.8\%, \(P = 0.021\)). In addition, for the laboratory results, patients with ISR had increased serum VLDL-C and TG levels compared with those without ISR (0.64 \(vs\) 0.51 mmol/L, \(P = 0.014\); 1.83 \(vs\) 1.69 mmol/L, \(P = 0.027\)), the levels of UA were also higher in ISR group than non-ISR group (364.67 \(vs\) 317.66 mmol/L, \(P = 0.036\)). But the level of TC, LDL-C, HDL-C, GLU, CRP, total bilirubin and red cell distribution width (RDW) were similar between the two groups. The use of drugs was also showed no significant difference.

#### 3.2 Baseline angiographic characteristics

Baseline angiographic and procedural characteristics in 368 patients with 550 lesions were shown in Table 2. Patients in the ISR group had more numbers of target vessel lesions compared with non-ISR group (1.70 \(vs\) 1.45, \(P = 0.021\)). The prevalence of multi-vessel disease (\(\geq 2\) vessels)
Table 1. Baseline clinical characteristics of study population.

| Characteristics     | ISR (n = 74) | Non-ISR (n = 294) | P values |
|---------------------|-------------|-------------------|---------|
| Age, yrs            | 56.61±10.37 | 59.37±10.05       | 0.127   |
| Male                | 56 (75.7%)  | 204 (69.4%)       | 0.453   |
| BMI, kg/m²          | 25.98±3.26  | 26.72±3.12        | 0.201   |
| SBP, mmHg           | 128.14±18.86| 131.77±18.59      | 0.291   |
| DBP, mmHg           | 75.78±11.48 | 78.12±10.23       | 0.227   |
| Smoking             | 26 (35.1%)  | 128 (43.5%)       | 0.354   |
| Drinking            | 2 (2.7%)    | 50 (17.0%)        | 0.026   |
| Medical history     |             |                   |         |
| Hypertension        | 48 (64.9%)  | 192 (65.3%)       | 0.960   |
| Hyperlipidemia      | 40 (54.1%)  | 152 (51.7%)       | 0.798   |
| History of MI       | 6 (8.1%)    | 24 (8.2%)         | 1.000   |
| History of stroke   | 2 (2.7%)    | 40 (13.6%)        | 0.115   |
| Previous PCI        | 18 (24.3%)  | 26 (8.8%)         | 0.021   |
| Previous CAGB       | 2 (2.7%)    | 2 (0.7%)          | 0.862   |
| Family history of CAD | 14 (18.9%) | 54 (18.4%)        | 0.938   |
| Laboratory results  |             |                   |         |
| TG, mmol/L          | 1.83 (1.28, 3.08) | 1.69 (1.17, 2.47) | 0.027   |
| TC, mmol/L          | 4.55 ± 0.95 | 4.52 ± 1.14       | 0.885   |
| LDL-C, mmol/L       | 2.71 ± 0.81 | 2.93 ± 0.66       | 0.233   |
| HDL-C, mmol/L       | 0.91 ± 0.18 | 0.96 ± 0.25       | 0.285   |
| VLDL-C, mmol/L      | 0.64 (0.35, 1.18) | 0.51 (0.26, 0.80) | 0.014   |
| FBG, mmol/L         | 7.65 ± 2.38 | 7.65 ± 2.26       | 0.992   |
| HbA1c               | 7.67% ± 1.47% | 7.29% ± 1.33%     | 0.128   |
| CRP, mg/L           | 2.31 (1.05, 3.72) | 2.34 (0.90, 4.25) | 0.933   |
| Creatinine, μmol/L  | 73.35 ± 18.50 | 75.89 ± 18.15     | 0.449   |
| GFR, mL/min         | 110.66 ± 32.25 | 102.17 ± 28.96    | 0.121   |
| UA, μmol/L          | 364.67 ± 133.15 | 317.66 ± 124.17   | 0.036   |
| TB, μmol/L          | 13.01 (8.38, 15.60) | 13.24 (9.31, 17.44) | 0.093   |
| DB, μmol/L          | 3.46 (2.03, 4.63) | 3.67 (2.64, 7.73) | 0.359   |
| RDW                  | 12.49% ± 0.77% | 12.49% ± 0.80%    | 0.977   |
| Platelet count, ×10^9/L | 205.10 ± 57.17 | 203.20 ± 64.65    | 0.874   |
| LVEF                 | 61.30% ± 7.76% | 62.01% ± 8.12%    | 0.664   |
| Medical treatment    |             |                   |         |
| Statins             | 66 (89.2%)  | 274 (93.2%)       | 0.635   |
| Aspirin             | 74 (100%)   | 288 (98.0%)       | 0.881   |
| β-Blocker           | 58 (78.4%)  | 220 (74.8%)       | 0.654   |
| Clopidogrel         | 72 (97.3%)  | 292 (99.3%)       | 0.862   |
| Insulin             | 18 (24.3%)  | 66 (22.4%)        | 0.808   |
| ACEI                | 28 (37.8%)  | 112 (38.1%)       | 0.977   |
| ARB                 | 6 (8.1%)    | 46 (15.8%)        | 0.234   |

Continuous variables are expressed as mean ± SD in case of normal distribution or as median (interquartile ranges) in case of skewed distribution. Categorical variables are presented as n (%) or distribution or as median (interquartile ranges) in case of skewed distribution. Categorical variables are presented as n (%). ACEI: angiotensin converting enzyme inhibitor; AGB: angiotensin receptor blocker; BMI: body mass index; CAGB: coronary artery bypass grafting; CAD: coronary artery disease; CRP: C-reactive protein; DB: direct bilirubin; DBP: diastolic blood pressure; FBG: fasting blood glucose; GFR: glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; ISR: in-stent restenosis; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: Percutaneous coronary intervention; RDW: red cell distribution width; SBP: systolic blood pressure; TB: total bilirubin; TC: total cholesterol; TG: triglyceride; UA: uric acid; VLDL-C: very low density lipoprotein cholesterol.

Table 2. Baseline angiographic characteristics of study population.

| Characteristics     | ISR (n = 74) | Non-ISR (n = 294) | P values |
|---------------------|-------------|-------------------|---------|
| Number of target vessels | 1.70 ± 0.66 | 1.45 ± 0.58       | 0.021   |
| One                 | 30 (40.5%)  | 174 (59.2%)       | 0.041   |
| Two                 | 36 (48.6%)  | 108 (36.7%)       | 0.184   |
| Three               | 8 (10.8%)   | 12 (4.1%)         | 0.227   |
| Multivessel disease | 44 (59.5%)  | 120 (40.8%)       | 0.041   |
| Target vessels      |             |                   |         |
| LM                  | 0           | 18 (6.1%)         | 0.264   |
| LAD                 | 52 (70.3%)  | 172 (58.5%)       | 0.190   |
| LCX                 | 34 (45.9%)  | 114 (38.8%)       | 0.427   |
| RCA                 | 40 (51.4%)  | 120 (40.8%)       | 0.147   |
| SYNTAX score        | 15.00       | 11.00             | 0.022   |
| Minimal stent diameter, mm | 2.81 ± 0.41 | 2.83 ± 0.45       | 0.849   |
| Stent length, mm    | 22.41 ± 4.37 | 21.32 ± 5.62      | 0.272   |

Continuous variables are expressed as mean ± SD in case of normal distribution or as median (interquartile ranges) in case of skewed distribution. Categorical variables are presented as n (%). ISR: in-stent restenosis; LAD: left anterior descending; LCX: left circumflex artery; LM: left main; RCA: right coronary artery; SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery.

was significantly higher in the ISR group than in the non-ISR group (59.5% vs. 40.8%, P = 0.041). The SYNTAX score was also significantly higher in the ISR group than in the non-ISR group (15.0 vs. 11.0, P = 0.022). The other basic angiographic information like target vessels, minimal stent diameter and stent length showed no real difference between the two groups.

3.3 Predictors of ISR in diabetes

In the multivariate Cox’s proportional hazards regression, after adjusting for traditional risk factors, lipid profiles, angiographic factors, medical history, and other biomarkers, the VLDL-C level, the UA level, SYNTAX score and previous PCI were identified as the independent predictors associated with ISR in diabetic patients (Figure 1). The HR for the occurrence of ISR associated with VLDL-C level was 1.85 (95% CI: 1.24–2.77, P = 0.002). For SYNTAX score (per 5 increments) and UA level (per 50 μmol/L increments), the HR was 1.34 (95% CI: 1.03–1.74, P = 0.031) and 1.19 (95% CI: 1.05–1.34, P = 0.006), respectively. A significantly higher proportion of patients had ISR in patients with the history of PCI (HR = 3.43, 95% CI: 1.57–7.80, P = 0.003). The ROC curve was used to measure the predictive values of the Cox’s regression model, and the AUC was 0.710 (95% CI: 0.607–0.813, P < 0.001) which
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Figure 1. Independent predictors of ISR in patients with diabetes mellitus after PCI by multivariate Cox’s proportional hazards regression model. ISR: in-stent restenosis; PCI: percutaneous coronary intervention; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; VLDL-C: very low density lipoprotein cholesterol.

Diabetes had been considered as a coronary disease equivalent condition. Patients with DM commonly had an increased risk of CAD with more severe disease phenotypes and had a poorer prognosis and higher mortality than non-diabetic patients. Increasing evidences suggested that DM was a major risk factor for ISR. A recent meta-analysis including 9578 total patients and 2667 DM patients showed that there was significant association between DM and ISR (OR = 1.70, 95% CI: 1.53–1.89). As the clinical situation of CAD patients combined with DM was worse than ordinary CAD patients, it became significant to find reliable factors to predict the risk of ISR, especially in the subpopulation of DM patients.

A recent multi-center study showed that the prevalence of dyslipidemia had reached up to 67.1% in DM patients in China. It is uniquely manifested by high level of TG and low level of HDL-C in DM patients, while the LDL-C level was not usually raised. Among the various components of serum lipids, VLDL-C was synthesized and secreted by hepatic cell, and it was the major lipoprotein of triglycerides-rich lipoprotein (TGRL), which was rich in 55% TG and 20% cholesterol. Additionally, current guidelines increasingly focused on reducing Non-HDL-C as the primary target of lipid-lowering therapy, which was mainly including LDL-C and VLDL-C. As a result, more and more researchers paid attention to the potential atherogenic effect of VLDL-C. Basic medicine experiments have shown that VLDL could penetrate the arterial intima and be taken up by macrophages, and then eventually resulted in cholesterol accumulation, which would promote the occurrence and development of atherosclerosis. Clinical observation studies in humans also indicated that the elevated levels of VLDL-C could increase the risk of CHD and have been regarded as an independent risk factor of CHD. For diabetic patients after PCI, most previous studies showed that there was no significant difference between the

Table 1. Predictors of ISR and HR (95% CI) P values

| Predictors of ISR                      | HR (95% CI) | P values |
|---------------------------------------|------------|----------|
| VLDL-C, mmol/L                        | 1.85 (1.24–2.77) | 0.002    |
| SYNTAX score, per 5 increments        | 1.34 (1.03–1.74) | 0.031    |
| Uric acid, per 50 μmol/L increments  | 1.19 (1.05–1.34) | 0.006    |
| Previous PCI                          | 3.43 (1.51–7.80) | 0.003    |

Figure 2. Receiver operating characteristics curve analysis for the prediction of the Cox’s regression model. AUC: area under the receiver operating characteristics curve.

showed a good predictive accuracy for the occurrence of ISR in diabetic patients (Figure 2).

4 Discussion

The results of this study showed that the occurrence rate of ISR reached up to 20% in diabetic patients after undergoing DES implantation. Patients with ISR had a significant increase of VLDL-C, UA levels and higher SYNTAX score compared with non-ISR patients. Multivariable analysis showed that even after adjustment for potential clinical variables and angiographic factors, the elevated baseline level of VLDL-C and UA, higher SYNTAX score and the history of previous PCI were identified to be independent predictors of ISR in patients with DM after coronary DES implantation.

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ISR and Non-ISR group in terms of the levels of TC, LDL-C and HDL-C. However, these studies always ignored the potential difference of VLDL-C level in diabetic patients. Similarly, no significant differences were observed between the ISR and non-ISR group in terms of the levels of TC, LDL-C and HDL-C in our study, but patients with ISR had higher VLDL-C and TG levels compared with those without ISR. Considering VLDL-C level was highly positive in correlation with TG, they were together entered into the multivariate regression model using the stepwise method after adjusting for traditional risk factors and other lipid profiles, and VLDL-C was identified as an independent predictor associated with ISR in diabetic patients but not TG (VLDL-C, HR = 1.85, 95% CI: 1.24–2.77, P = 0.002). This suggested that VLDL-C might be the most major lipid profiles in promoting the occurrence and development of ISR among diabetic patients who usually had high level of TG. The American Diabetes Association and the American College of Cardiology recommended that non-HDL-C target goals should be < 130 mg/dL for diabetic patients with overt CVD, as well as those without overt CVD. This is due to the fact that LDL-C was not usually elevated in diabetes, thus leaving VLDL-C the major therapeutic goal in the lipid management among patients with DM after PCI.

Hyperuricemia was not only critical to gout, but also found to be linked with diabetes and associated with metabolic syndrome. The elevated baseline serum UA was in fact an independent risk factor in the development of insulin resistance and subsequent diabetes. Previous study had found that high preprocedural UA level was a powerful and independent predictor of bare metal stent restenosis in patients with stable or unstable angina pectoris (OR = 1.07, 95% CI: 1.03–1.12, P = 0.003). Similarly, our study indicated that the preprocedural UA level (per 50 mmol/L increments) was significantly associated with further ISR in diabetes who underwent successful DES implantation (HR = 1.19, 95% CI: 1.05–1.34, P = 0.006). Findings of experimental and clinical studies had proved the proinflammatory properties of UA, which was positively related with the level of TNF-α and IL-6 and it promoted the secretion of CRP in human vascular cells. UA could also stimulate vascular smooth muscle cell (SMC) proliferation and the neointimal formation in the surface of the stent. Persistence of inflammatory stimuli and subsequent cellular proliferation within vulnerable plaque was considered to play an important role in the occurrence of ISR after PCI. Based on existing evidences, it was speculated that the UA might increase the risk for ISR through increasing proinflammatory status and proliferation of vascular SMC. Therefore, the level of UA could serve as a meaningful marker in PCI patients especially in diabetics.

SYNTAX score was an angiographic scoring system to objectively grade the complexity of the coronary anatomy, which was initially introduced in 2005 and validated by a stage III clinical trial. Subsequent reports had demonstrated that the SYNTAX score could be able to stratify patients with complex coronary diseases and had a prognostic value to predict the risk of short- and long-term major ischemic events in patients undergoing PCI. Considering the diabetic patients had more sever coronary atherosclerosis with small and diffusely lesions, our findings indicated that SYNTAX score (per 5 increments) was independently associated with ISR of target lesions (HR = 1.34, 95% CI: 1.03–1.74, P = 0.031) in patients with DM, suggesting that greater anatomic complexity of CAD conferred a higher risk of progression of atherosclerosis and ISR after PCI. Previous studies have found that the SYNTAX score was an independent predictor of target vessel revascularization (TVR) (OR = 1.03, 95% CI: 1.02–1.05, P < 0.0001) and any revascularization (OR = 1.04, 95% CI: 1.03–1.05, P < 0.0001) in patients treated with DES, even after correcting for clinical variables. Those present findings were consistent with a report indicating that lesion progression occurred more rapidly in diabetic patients with complex lesions than in diabetic patients with simple lesions. In this way, as a surrogate marker of disease burden before PCI based on the location and characteristics of coronary lesions, SYNTAX score might provide new incremental value to assess the risk of ISR in diabetic patients.

Recent reports confirmed that the history of previous PCI was identified as an independent predictor of TVR (OR = 1.90, 95% CI: 1.49–2.41, P < 0.0001) and any revascularization (OR = 1.64, 95% CI: 1.28–2.11, P < 0.0001), suggesting that the preoperative factors affecting coronary atherosclerosis were still working in patients who underwent PCI. Our Study also demonstrated that the diabetic patients with a history of PCI had a higher risk of ISR after DES implantation (HR = 3.43, 95% CI: 1.57–7.80, P = 0.003), which was consistent with those of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study findings with respect to the impact of diabetes and previous PCI on any revascularization (HR = 2.03, 95% CI: 1.15–3.59, P = 0.02).

Some limitations of the present study had to be acknowledged. First, the study was only a single-center study with a small sample size, which would have weakened the statistical power of the conclusions. Although the required number of observations had been a priori calculated by power analysis, additional large-scale prospective cohort studies at multiple centers were needed to confirm our re-
sults in additional patient cohorts before any clinical conclusions could be drawn. Second, in the present study, 92% patients had taken statin medication, which might have effect on the lipid profile levels, such as TC, LDL-C and HDL-C. However, to the best of our knowledge, this was the first report to demonstrate the level of VLDL-C was significantly associated with the risk ISR in diabetic patients even when other lipid profiles like TC, LDL-C were controlled by statin medication. This suggested that VLDL-C might play a profound role in the development of ISR and should be given more attention as a new target goal for lipid-lowering treatment among patients with DM. Third, duration of DM had been associated to poor clinical outcomes of CAD. The present study did not record patient-reported duration of DM, so it was not possible to investigate the influence of the DM duration on the development of ISR. Forth, our study only included patients who underwent the second angiography due to the progression of treated target lesions rather than untreated non-target lesions, which made our results more applicable for the specific subpopulation for better prevention of ISR.

In summary, our study provided evidence that the increased serum VLDL-C and UA level, higher SYNTAX score and the history of previous PCI were strong independent predictors of ISR in patients with DM after coronary DES implantation. Predicting the risk of ISR in diabetic patients after PCI allowed physicians to proactively intervene in ways that would lower the risk for the management of these patients, such as prescribing aggressive lipid-lowering and UA-lowering medication to reduce the circulating level of VLDL-C and UA. SYNTAX score could also be well-used to comprehensively evaluate the degree of coronary artery lesions and the risk to develop ISR in the subpopulation of DM patients.

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