Original Article

Elevated Levels of Very Low-density Lipoprotein Cholesterol Independently Associated with In-stent Restenosis in Diabetic Patients after Drug-eluting Stent Implantation

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Abstract

Background: High rate of in-stent restenosis (ISR) remained an unsolved clinical problem in clinical practice, especially among patients with diabetes mellitus (DM). Diabetic patients often had hypertriglyceridemia with elevated levels of very low-density lipoprotein cholesterol (VLDL-C). Increasing evidence suggested that VLDL-C was known as a significant risk factor for atherosclerosis and had been recommended as a treatment target by current dyslipidemia guidelines. However, the role of VLDL-C in the occurrence and development of ISR in coronary artery disease (CAD) patients with DM had not been studied. The aim of this study was to evaluate the association between the elevated levels of VLDL-C and the risk of ISR in CAD patients with DM.

Methods: A total of 1390 diabetic patients, who underwent coronary drug-eluting stent (DES) implantation at Beijing Anzhen Hospital and followed up by angiography within 6–24 months, were consecutively enrolled. Patients' demographic and clinical characteristics, including age, gender, CAD risk factors, family history, life style, medical history, and coronary angiographic information, were collected carefully at baseline percutaneous coronary intervention and follow-up angiography. Multivariate Cox's proportional hazards regression modeling using the step-wise method (entry, 0.05; removal, 0.05) was used to determine the independent risk associated with ISR in diabetic patients.

Results: Finally, 1206 of patients were included in this study. ISR occurred in 132/1206 diabetic patients (10.9%) by follow-up angiography. Patients with ISR had elevated median serum VLDL-C levels compared with those without ISR (0.65 mmol/L vs. 0.52 mmol/L, $P = 0.030$). The multivariate regression analysis showed that VLDL-C was significantly associated with the risk of ISR in diabetic CAD patients (hazard ratio [*HR*] = 1.15, 95% confidence interval [*CI*]: 1.03–1.29, $P = 0.017$). The *HR* for the risk of ISR associated with VLDL-C level ≥0.52 mmol/L was 3.01 (95% *CI*: 1.24–7.34, $P = 0.015$).

Conclusion: The elevated level of serum VLDL-C was a significant and independent risk factor for ISR in diabetic CAD patients after coronary DES implantation.

Key words: Diabetes Mellitus; Drug-eluting Stent Implantation; In-stent Restenosis; Very Low-Density Lipoprotein Cholesterol

Introduction

Percutaneous coronary intervention (PCI) has become the major therapeutic procedure for coronary artery disease (CAD) in recent 30 years.[1,2] However, several large-scale clinical trials had confirmed that even in the drug-eluting stent (DES) era, the occurrence rate of in-stent restenosis (ISR) after coronary stent implantation still ranged from 3% to 20%.[3] Especially

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among patients with diabetes mellitus (DM), the risk of developing ISR after PCI appeared to be 2–4 times higher compared with nondiabetic patients.[4,5] What's more, about 67% of diabetic patients had dyslipidemia and young-onset type 2 DM (T2DM) is increasing in China,[6] which was uniquely manifested by the high levels of very low-density lipoprotein cholesterol (VLDL-C) and triglyceride (TG), but the usually normal level of low-density lipoprotein cholesterol (LDL-C).[7] Of which, accumulating evidence suggested that VLDL-C was a significant risk factor for atherosclerosis and cardiovascular disease (CVD).[8-10] Moreover, it had been recommended as a clinical target of lipid-lowering therapy by current dyslipidemia guidelines.[11,12] Thus, more and more researchers and cardiologists paid attention to the potential atherogenic effect of VLDL-C.

To the best of our knowledge, most previous related studies focused on exploring the risk factor of ISR among general CAD patients rather than diabetic CAD patients.[13-15] Therefore, the aim of this study was to evaluate the association between the VLDL-C levels and the ISR risk in diabetic patients after undergoing DES implantation.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Informed written consent was obtained from all patients before their enrollment in this study.

Study patients

A total of 1390 CAD patients with T2DM, who underwent successful coronary DES implantation in the 1st, 3rd and 12th cardiovascular wards of Beijing Anzhen Hospital (Beijing, China) from January 2012 to December 2013 and followed up by angiography within 6–24 months, were consecutively enrolled. Follow-up angiography was prespecified by the study protocol, all patients were asked for received follow-up angiography for re-examining whether ISR was developed or not. Among these patients, 374 of patients (26.9%) received follow-up angiography driven by clinical symptom. The patients should also meet the following inclusion criteria: (1) No history of coronary artery bypass grafting, previous PCI, heart failure, or tumor; (2) normal liver and renal function, no active infection and inflammation; (3) no contraindications to aspirin, clopidogrel, statin, or heparin; and (4) taking statin or other lipid-lowering drugs over 3 months at the baseline. Patients without sufficient clinical and angiographic data at baseline and follow-up were excluded from the study.

Stent implantation

All patients received DES implantation in our catheterization center. Stent implantation was performed according to the standard guidelines, and stents were selected by experienced interventional cardiologists. During the procedure, patients received a bolus of 100 U/kg heparin, with a repeated bolus of 2000 U heparin to maintain the activated clotting time of ≥300 s. All patients received aspirin (100 mg/d) and clopidogrel (300 mg loading dose, followed by 75 mg/d for at least 12 months). When ISR was diagnosed by the follow-up angiography during the study period, patients were treated with re-DES implantation. The successful procedure was defined as a reduction of the stenosis to <10% residual narrowing, thrombolysis in myocardial infarction flow Grade III, with improvement in ischemic symptoms, and without major procedure related complications.[16]

Data collection

Patients' demographic and clinical characteristics, including age, gender, CAD risk factors, family history, life style, medical history, and coronary angiographic information, were collected carefully at baseline PCI and follow-up angiography. During the physical examination, anthropometric indices, such as weight, height, and blood pressure, were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Data regarding stent and angiograph such as the minimal stent diameter, average stent length, and the numbers of target vessels were also recorded by two experienced cardiologists at baseline and follow-up for coronary angiography analysis.

Laboratory analysis

Venous blood samples were collected after an overnight for testing the lipid profiles, hemoglobin A1c (HbA1c), fasting blood glucose (FBG), high-sensitivity C-reactive protein, uric acid (UA) levels, and other biomarkers using standard laboratory method at baseline PCI and follow-up angiography. The HbA1c was tested using ion exchange high-performance liquid chromatography method. The total cholesterol (TC), TG, FBG, and UA were determined according to enzymatic methods. The LDL-C and high-density lipoprotein cholesterol (HDL-C) levels were measured by homogeneous assays. The VLDL-C levels were calculated as TC − LDL-C − HDL-C according to the recommendation of dyslipidemia guidelines.[11,12]

Disease definitions

The primary end point of the study was the occurrence of ISR. ISR was defined as a diameter stenosis of ≥50% occurring in the segment inside the stent or a 5 mm proximal or distal to the stent at follow-up angiography.[17,18] According to whether ISR was detected, patients were classified into two groups: the ISR group and the non-ISR group. Target lesion was considered to be the most severe narrowing vessel, identified by angiographic appearance with electrocardiograph changes. Multivessel disease was defined as a diameter stenosis of ≥50% occurring in two or more vessels.

T2DM was defined as either a previous diagnosis of DM treated with diet, oral agents or insulin or a new diagnosis of DM if FBG ≥7.0 mmol/L on two occasions.[19] Hypertension was defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or the use of the

antihypertensive treatment in the past 2 weeks.[20] The severity of coronary artery lesions was quantified with Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score,[21] which was calculated using the online calculator for SYNTAX score.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) in the case of normal distribution, and differences between the ISR group and the non-ISR group were determined by two-independent samples *t*-test. Data were expressed as median (P_{25}, P_{75}) in the case of skewed distribution and compared using the Mann-Whitney *U*-test. Categorical variables were presented as counts (percentages) and compared using Chi-square test.

The potential baseline variables which had either a clinically plausible relation with ISR or appeared to be imbalanced between ISR and non-ISR groups in univariate analysis were selected into multivariate Cox's proportional hazards regression modeling using the step-wise method (entry, 0.05; removal, 0.05) to determine the independent risk associated with ISR in diabetic patients. The variables included traditional risk factors, lipid profiles, angiographic factors, SYNTAX score, multivessel disease, medical treatment, and other biomarkers such as HbA1c, creatinine, and UA. VLDL-C levels were assumed to be a continuous variable in the model 1 and a categorical variable in the model 2. The hazard ratio (*HR*) and 95% confidence interval (*CI*) of the independent predictors were calculated to estimate the adjusted risk for ISR in diabetic patients.

The predictive accuracy of the VLDL-C model for predicting the risk of ISR was evaluated using the area under the receiver operating characteristics curve (AUC) (C-statistics). Moreover, the receiver operating characteristic curves (ROC) were analyzed to assess the optimal cutoff value of the VLDL-C level for predicting the risk of ISR. The optimal cutoff point was calculated using the Youden index with both maximum sensitivity and specificity. Statistical analyses were performed using SPSS software for Windows (version 22.0, SPSS Inc., Chicago, Illinois, USA). A value of $P < 0.05$ (two-sided) was considered statistically significant.

Results

Finally, a total of 1206 patients (378 females and 828 males) were included in this study, with a mean age of 59.3 ± 9.7 years. The results of angiography showed that ISR occurred in 132/1206 diabetic patients (10.9%). According to whether ISR was detected, patients were divided into ISR group ($n = 132$) and non-ISR group ($n = 1074$).

Baseline clinical characteristics

The baseline clinical characteristics were displayed in Table 1. There were no significant differences in age, gender, BMI, smoking, drinking, and medical history and treatment between ISR and non-ISR groups (all $P > 0.05$). Patients with ISR had increased median serum VLDL-C levels compared with those without ISR (0.65 mmol/L vs. 0.52 mmol/L, $P = 0.030$). In addition, patients in the ISR group had significantly higher level of HbA1c, creatinine, and UA than those in the non-ISR group (all $P < 0.05$).

Baseline angiographic characteristics

Baseline angiographic characteristics were shown in Table 2. There were 1660 target vessel lesions in 1206 patients. Patients in the ISR group had more median numbers of target vessel lesions compared with patients in non-ISR group (1.6 vs. 1.3, $P < 0.001$). The prevalence of multi-vessel disease (≥2 vessels) was higher in ISR group than that in the non-ISR group (60.6% vs. 37.8%, $P < 0.001$). The median SYNTAX score was also significantly higher in the ISR group than that in the non-ISR group (13.00 vs. 11.00, $P = 0.040$).

Association of very low-density lipoprotein cholesterol with in-stent restenosis

In the multivariate model 1, after adjusting for other confounding factors, the VLDL-C level was identified as one of the independent risk factors associated with ISR in diabetic CAD patients [Table 3]. The *HR* of VLDL-C for the risk of ISR was 1.15 (95% *CI*: 1.03–1.29, $P = 0.017$). For other risk factors, such as SYNTAX score (per 5 score increments) and HbA1c, the *HR* was 1.44 (95% *CI*: 1.12–1.86, $P = 0.005$) and 1.47 (95% *CI*: 1.07–2.02, $P = 0.017$), respectively.

Ability of receiver operating characteristic curve analysis of very low-density lipoprotein cholesterol to predict in-stent restenosis

The ROC curve analysis indicated that the AUC was 0.71 (95% *CI*: 0.63–0.80, $P < 0.001$), which showed a good predictive accuracy of VLDL-C model for the risk of ISR in diabetic CAD patients [Figure 1]. The baseline VLDL-C level at 0.52 mmol/L (200 mg/L) was identified

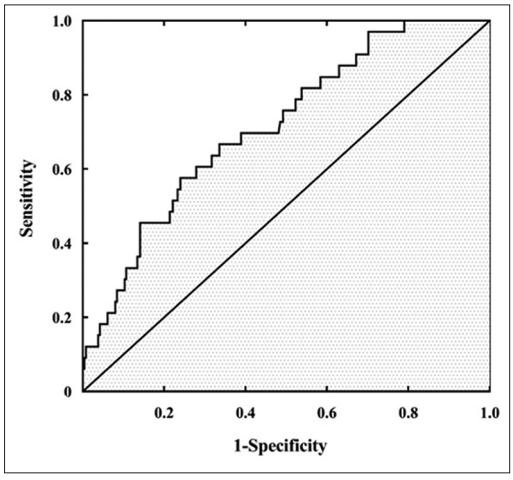

Figure 1: Receiver operating characteristics curve analysis for the predictive value of VLDL-C level in predicting the risk of ISR (AUC: 0.71; 95% *CI*: 0.63–0.80; $P < 0.001$). ISR: In-stent restenosis; VLDL-C: Very low-density lipoprotein cholesterol; ACU: Area under the receiver operating characteristics curve; *CI*: Confidence interval.

Table 1: Baseline clinical characteristics of all patients in this study

Characteristics	Total patients (n = 1206)	ISR group (n = 132)	Non-ISR group (n = 1074)	Statistical values	P
Age (years)	59.3 ± 9.7	59.1 ± 9.9	59.3 ± 9.7	0.247	0.805
Male	828 (68.7)	96 (72.7)	732 (68.2)	1.141	0.285
BMI (kg/m^2)	26.31 ± 3.07	26.25 ± 2.83	26.32 ± 3.10	0.247	0.805
SBP (mmHg)	132.56 ± 17.42	136.00 ± 18.27	132.12 ± 17.29	2.418	0.015
DBP (mmHg)	78.76 ± 9.94	79.27 ± 11.61	78.69 ± 9.73	0.643	0.520
Smoking	484 (40.1)	44 (33.3)	440 (41.0)	2.852	0.091
Drinking	196 (16.3)	20 (15.2)	176 (16.4)	0.132	0.716
Medical history					
Hypertension	848 (70.3)	84 (63.6)	764 (71.1)	3.168	0.075
Hyperlipidemia	584 (48.4)	56 (42.4)	528 (49.2)	2.137	0.144
History of MI	104 (8.6)	16 (12.1)	88 (8.2)	2.301	0.129
History of stroke	108 (9.0)	8 (6.1)	100 (9.3)	1.523	0.217
Family history of CAD	196 (16.3)	28 (21.2)	168 (15.6)	2.679	0.102
Laboratory results					
TG (mmol/L)	1.57 (1.22, 2.29)	1.58 (1.16, 1.94)	1.57 (1.23, 2.34)	0.754	0.621
TC (mmol/L)	4.45 ± 1.08	4.54 ± 1.07	4.44 ± 1.09	0.997	0.319
LDL-C (mmol/L)	2.86 ± 0.92	2.87 ± 0.94	2.86 ± 0.92	0.118	0.906
HDL-C (mmol/L)	1.01 ± 0.25	1.02 ± 0.24	1.01 ± 0.26	0.420	0.674
VLDL-C (mmol/L)	0.53 (0.33, 0.76)	0.65 (0.38, 0.77)	0.52 (0.32, 0.76)	2.806	0.030
FBG (mmol/L)	7.84 ± 2.62	7.98 ± 2.56	7.82 ± 2.63	0.661	0.508
HbA1c (%)	7.32 ± 1.22	7.66 ± 0.92	7.28 ± 1.25	3.381	0.001
hs-CRP (mg/L)	2.60 (0.90, 4.98)	2.65 (1.05, 9.80)	2.44 (0.89, 4.71)	0.657	0.511
Creatinine (μmol/L)	78.06 ± 20.14	78.54 ± 20.26	74.24 ± 19.04	2.316	0.021
UA (μmol/L)	342.97 ± 92.92	345.78 ± 91.82	320.66 ± 99.91	2.937	0.003
Medical treatment					
Aspirin	1164 (96.5)	132 (100.0)	1032 (96.1)	2.579	0.108
β-blocker	900 (74.6)	104 (78.8)	796 (74.1)	1.355	0.224
Clopidogrel	1180 (97.8)	132 (100.0)	1048 (97.6)	0.841	0.359
Insulin	276 (22.9)	24 (18.2)	252 (23.5)	1.858	0.173
ACEI	388 (32.2)	40 (30.3)	348 (32.4)	0.237	0.626
ARB	276 (22.9)	28 (21.2)	248 (23.1)	0.235	0.628
Clinical presentation					
Stable angina pectoris	189 (15.7)	19 (14.4)	170 (15.8)	0.183	0.669
Unstable angina pectoris	649 (53.8)	74 (56.1)	575 (53.5)	0.301	0.583
STEMI	184 (15.3)	21 (15.9)	163 (15.2)	0.049	0.825
Non-STEMI	139 (11.5)	14 (10.6)	125 (11.6)	0.123	0.726
Asymptomatic CAD	45 (3.7)	4 (3.0)	41 (3.8)	0.203	0.652

Continuous variables were expressed as mean ± SD in case of normal distribution and compared between ISR and non-ISR groups by two-independent samples t-test. Data were expressed as median (P_{25}, P_{75}) in case of skewed distribution and compared using the Mann-Whitney U-test. Categorical variables are presented as n (%) and compared using Chi-square test. ISR: In-stent restenosis; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MI: Myocardial infraction; CAD: Coronary artery disease; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; FBG: Fasting blood glucose; hs-CRP: High-sensitivity C-reactive protein; UA: Uric acid; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; SD: Standard deviation; HbA1c: Hemoglobin A1c; STEMI: ST-elevation myocardial infarction.

as the optimal cutoff point. The *HR* for the risk of ISR associated with VLDL-C level ≥0.52 mmol/L was 3.01 (95% *CI*: 1.24–7.34, P = 0.015) in model 2 [Table 3].

Discussion

The results of this study showed that the occurrence rate of ISR was 10.9% (132/1206) in diabetic CAD patients after undergoing DES implantation within 2 years. The results of this study indicated that the elevated level of serum VLDL-C was an independent risk factor for ISR among diabetic CAD patients.

DM had been recognized as a coronary disease equivalent condition. Patients with DM often had a higher risk of ISR and thromboembolic events than nondiabetic patients.[4,5,22,23] A recent meta-analysis, including 9578 total patients and 2667 DM patients, showed that there was a significant association between DM and ISR (odds ratio [*OR*] = 1.70, 95% *CI*: 1.53–1.89).[5] Diabetic patients had more complex coronary lesion anatomy with small and diffusely diseased vessels.[24] Moreover, they often had dyslipidemia and systemic prothrombotic state related to the activation of the platelet aggregation and coagulation systems.[6,25] Altogether, these made diabetic patients a challenging subpopulation who

Table 2: Baseline angiographic characteristics of study population

Characteristics	Total patients (n = 1206)	ISR group (n = 132)	Non-ISR group (n = 1074)	Statistical values	P
Number of target vessels	1.4 ± 0.6	1.6 ± 0.7	1.3 ± 0.5	6.190	<0.001
1	720 (59.7)	52 (39.4)	668 (62.2)	28.840	<0.001
Multivessel disease*	486 (40.3)	80 (60.6)	406 (37.8)	25.407	<0.001
2	416 (34.5)	64 (48.5)	352 (32.8)		
3	70 (5.8)	16 (12.1)	54 (5.0)		
Target vessels					
LM	52 (4.3)	0	52 (4.8)	3.791	0.052
LAD	736 (61.0)	100 (75.8)	636 (59.2)	13.521	<0.001
LCX	396 (32.8)	52 (39.4)	344 (32.0)	2.891	0.089
RCA	476 (39.5)	64 (48.5)	412 (38.4)	5.043	0.025
SYNTAX score	11.00 (8.00, 17.00)	13.00 (9.50, 20.25)	11.00 (7.00, 16.00)	2.057	0.040
Minimal stent diameter (mm)	2.91 ± 0.62	2.93 ± 0.61	2.90 ± 0.62	0.526	0.599
Stent length (mm)	22.76 ± 8.07	22.72 ± 5.51	22.76 ± 8.35	0.054	0.957

Continuous variables were expressed as mean ± SD in case of normal distribution and compared between ISR and non-ISR groups by two-independent samples t-test. Data were expressed as median (P_{25}, P_{75}) in case of skewed distribution and compared using the Mann-Whitney U-test. Categorical variables are presented as n (%) and compared by Chi-square test. *Multivessel disease was defined as a diameter stenosis of ≥50% occurring in two or more vessels. ISR: In-stent restenosis; LM: Left main; LAD: Left anterior descending; LCX: Left circumflex artery; RCA: Right coronary artery; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; SD: Standard deviation; PCI: Percutaneous coronary intervention.

Table 3: Independent risk factors of ISR in CAD patients with DM after baseline PCI

Variables	*HR*	95% *CI*	*P*
Model 1			
VLDL-C (per 0.1 mmol/L)	1.15	1.03–1.29	0.017
SYNTAX score (per 5 score)	1.44	1.12–1.86	0.005
HbA1c (%)	1.47	1.07–2.02	0.017
Model 2			
VLDL-C			
<0.52 mmol/L	Reference	–	–
≥0.52 mmol/L	3.01	1.24–7.34	0.015
SYNTAX score (per 5 score)	1.48	1.14–1.91	0.003

Model l: VLDL-C was used as a continuous variable; Model 2: VLDL-C was used as a categorical variable. ISR: In-stent restenosis; CAD: Coronary artery disease; DM: Diabetes mellitus; PCI: Percutaneous coronary intervention; *HR*: Hazard ratio; 95% *CI*: 95% confidence interval; VLDL-C: Very low-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery.

should be given more specific treatment and management. Thus, it was very significant to find reliable factors to predict the risk of ISR, especially in diabetic patients.

A recent multicenter study showed that the prevalence of dyslipidemia had reached up to 67.1% in diabetic patients in China,[6] which was uniquely manifested by the high level of VLDL-C and TG, low level of HDL-C, but the usually normal level of LDL-C.[7] Increasing evidence indicated that triglycerides-rich lipoprotein (TGRL) was one of the most important residual risk factors of CVD beyond LDL-C.[10,26,27] The fasting serum TG was usually measured as the most common biomarker of TGRL. However, many prospective epidemiological studies suggested that serum TG might not capture the true extent of CVD risk, and failed to fully reflect the cholesterol content of VLDL.[9,28] The levels of VLDL-C could be considered as a potential superior biomarker of TGRL-related CVD risk than TG.[9,28] In addition, current guidelines increasingly focused on reducing Non-HDL-C (VLDL-C and LDL-C) as the primary target of lipid-lowering therapy.[11,12] Therefore, more and more researchers and cardiologists paid attention to the potential atherogenic effect of VLDL-C.

For diabetic patients after PCI, most previous studies showed that there was no significant difference between the ISR and non-ISR group in terms of the levels of TC, LDL-C, and HDL-C.[16] However, these studies always ignored the potential difference of VLDL-C levels, and no prior studies had ever examined the relationship of serum VLDL-C levels with ISR. 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 this study, but this study found that patients with ISR had significantly higher VLDL-C levels compared with those without ISR. VLDL-C was identified as an independent risk factor associated with ISR in diabetic patients. This suggested that VLDL-C might be the major lipid profiles in promoting the occurrence and development of ISR among diabetic patients beyond LDL-C and TG.

There were some proposed mechanisms for why VLDL-C might have causal relations to ISR beyond other lipids in diabetic patients. One of the established mechanisms underlying ISR was neo-atherosclerosis developing within neointima.[29] The neointima formation occurred on the surface of the stent within almost one year after PCI,[30] and the ISR was caused by the further progression of neo-arteriosclerosis after neointimal formation.[29,31] In diabetic patients with insulin resistant states, the levels of VLDL-C often raised at a high level because of increased hepatic VLDL production and failure to clear postprandial lipids.[28] Each VLDL particle could transport more cholesterol than each LDL particle[32] and it had already been found in the human intima and isolated from the

atherosclerotic lesion,[33,34] which directly suggested that VLDL could be taken up by macrophages in the arterial wall and made a crucial contribution to inflammation and atherosclerosis plaque. Persistence of inflammatory stimuli and cellular proliferation further promoted the development of ISR.[30]

Some limitations of the present study had to be acknowledged. First, this study was only a single-center study, which might weaken the statistical power of the conclusions. Although the required sample number of patients had been prior calculated by power analysis (estimated power = 96.8% using NCSS-PASS 11.0, USA), additional large-scale prospective cohort studies at multiple centers were also needed to confirm our results before any clinical conclusions could be drawn. Second, the hard endpoint of clinically-driven target vessel revascularization and target lesion revascularization, and major adverse cardiovascular events would be more appropriate to draw a credible conclusion. Our research team is now doing this to collect more patients with hard end points. Besides we did not do an intravascular ultrasound and optical coherence tomography at the beginning of the study design. In the future studies, we will add more related examination to further verify our results.

In summary, this study provided evidence that the elevated level of serum VLDL-C independently associated with the risk of ISR in CAD patients with DM after coronary DES implantation. It also needs to be further tested by larger studies with hard end point. Recognized the risk factors of ISR in advance among diabetic patients allowed physicians to proactively intervene in clinical practice for better management and prevention of ISR.

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Conflicts of interest

There are no conflicts of interest.

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