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Original Article

Impact of risk factors on intervened and non-intervened coronary lesions

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Abstract: Introduction: In-stent restenosis (ISR) and aggravated non-intervened coronary lesions (ANL) are two pivotal aspects of disease progression in patients with coronary artery disease (CAD). Established risk factors for both include hyperlipidemia, hypertension, diabetes, chronic kidney disease, and smoking. However, there is limited research on the comparative risk factors for the progression of these two aspects of progression. The aim of this study was to analyze and compare the different impacts of identical risk factors on ISR and ANL. Methods: This study enrolled a total of 510 patients with multiple coronary artery lesions who underwent repeated coronary angiography (CAG). All patients had previously undergone percutaneous coronary intervention (PCI) and presented non-intervened coronary lesions in addition to the previously intervened vessels. Results: After data analysis, it was determined that HbA1c (OR 1.229, 95% CI 1.022-1.477, P=0.028) and UA (OR 1.003, 95% CI 1.000-1.005, P=0.024) were identified as independent risk factors for ISR. Furthermore, HbA1c (OR 1.215, 95% CI 1.010-1.460, P=0.039), Scr (OR 1.007, 95% CI 1.003-1.017, P=0.009), and ApoB (OR 1.017, 95% CI 1.006-1.029, P=0.004) were identified as independent risk factors for ANL. The distribution of multiple blood lipid levels differed between the ANL only group and the ISR only group. Non-HDL-C (2.17 mmol/L vs. 2.44 mmol/L, P=0.007) and ApoB (63.5 mg/dL vs. 71.0 mg/dL, P=0.011) exhibited significantly higher values in the ANL only group compared to the ISR only group. Conclusions: Blood glucose levels and chronic kidney disease were identified as independent risk factors for both ISR and ANL, while elevated lipid levels were only significantly associated with ANL. In patients with non-intervened coronary lesions following PCI, it is crucial to assess the concentration of non-HDL-C and ApoB as they serve as significant risk factors.

Keywords: Progression of CAD, non-HDL-C, ApoB, blood glucose levels, chronic kidney disease

Introduction

Coronary artery disease (CAD) is a prominent cause of global mortality [1, 2]. With the advancement of coronary angiography (CAG) and percutaneous coronary intervention (PCI), intervention for complex coronary artery lesions has become more refined. In patients with multivessel coronary disease [2, 3], stenosis was treated based on the severity of the coronary artery lesions. Intervention therapy is recommended for unstable plaque or lesions with a diameter stenosis exceeding 70% (50% in the Left Main). Otherwise, the lesions can be temporarily treated with medication. Additional assessment tools such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR) can provide supplementary information beyond CAG, assisting the interventional cardiologists in determining optimal treatment strategies. These patients with multivessel coronary disease are also faced with two aspects of disease progression: in-stent restenosis (ISR) [4, 5] and aggravated non-intervened coronary lesions (ANL) [6, 7].

As the follow-up period extends, there is a progressive increase in the incidences of both aspects of disease progression. The cumulative incidence of ISR requiring revascularization within the first year was 7.3%, and this trend persisted without attenuation for up to 5 years (2.2%/year) [8]. The cumulative incidence of ANL progression requiring additional PCI therapy increased from 6-10% in the initial post-PCI year to 14-16% in the 2nd and 3rd years, and

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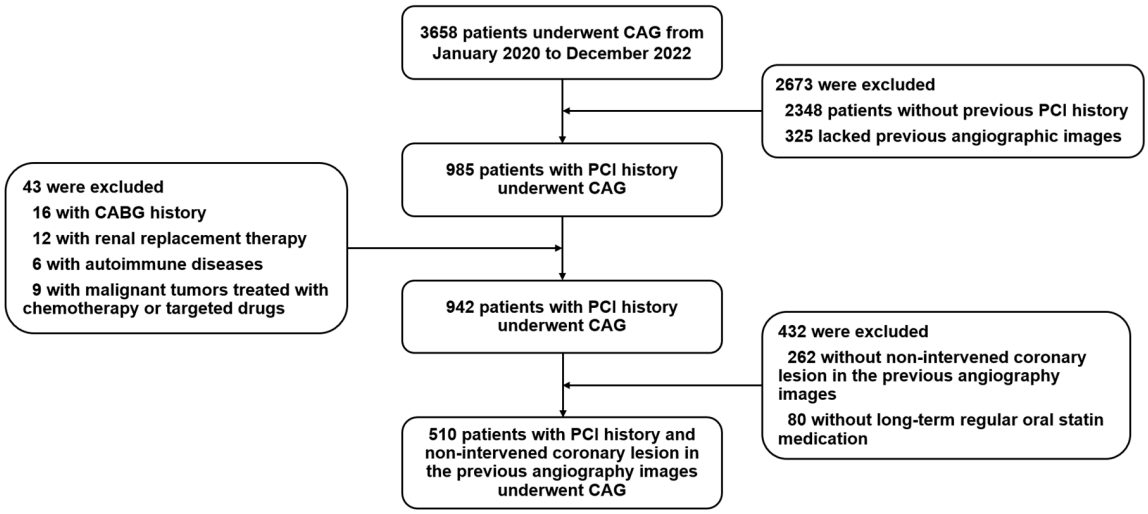

Figure 1. Study flowchart diagram.

approximately 18% in the 5th year [9-11]. Various mechanisms contribute to the development of ISR, with neointimal hyperplasia being the predominant long-term mechanism. Risk factors associated with CAD can lead to both intimal hyperplasia and neointimal hyperplasia. Previous studies have demonstrated that hyperlipidemia, hypertension, diabetes, chronic kidney disease, and smoking are risk factors for CAD and can contribute to the development of both ISR and ANL [12, 13]. However, limited research has been conducted on the disparities in risk factors between these two types of disease progression.

The aim of this study was to investigate patients with multivessel disease who underwent PCI and compare the impact of various risk factors, including lipid profiles, on both ISR and ANL.

Methods

Study population

This study is a retrospective trial. The enrolled patients met the following criteria: (1) prior history of drug-eluting stent (DES) implantation with non-intervened coronary lesions in vessels other than the target vessel; (2) underwent repeated CAG due to recurrent angina symptoms, positive treadmill exercise test, or coronary CTA revealing moderate to severe stenosis; (3) received long-term regular oral statin medication with lipid levels monitored post-PCI. Exclusion criteria encompassed patients with a history of CABG, renal replacement therapy, autoimmune diseases, or malignant tumors undergoing chemotherapy or targeted drug treatment.

From January 2020 to December 2022, a total of 3,658 patients underwent CAG. Among them, 1,310 patients had a history of previous PCI. A subset of 325 patients lacking prior angiographic images were excluded from the analysis. Additionally, 43 patients with a history of CABG, renal replacement therapy, autoimmune diseases, or undergoing chemotherapy or targeted drug treatment for malignant tumors were also excluded. Finally, the previous angiographic images of 942 patients were analyzed. Among this group, 510 patients exhibited non-intervened coronary lesions in their prior angiography images and received long-term regular oral statin medication (**Figure 1**).

Coronary angiography

Non-intervened coronary lesion is defined as a coronary artery with a diameter stenosis ranging from 40% to 60% as observed in the previous angiography, which can be temporarily managed through medication rather than intervention. ANL is assessed using a similar angiographic approach and is defined as a diameter stenosis of ≥70% requiring additional intervention during the current angiography [9-11]. ISR is defined as a narrowing within the stent with a diameter exceeds 50% of the vessel lumen

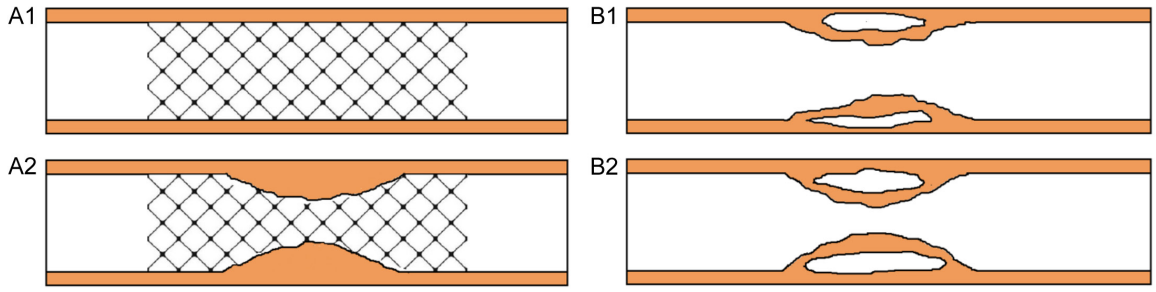

Figure 2. ISR and ANL. A: ISR; A1: previous angiography of ISR; A2: current angiography of ISR; B: ANL; B1: previous angiography of ANL; B2: current angiography of ANL. ISR: in-stent restenosis; ANL: aggravated non-intervened coronary lesion.

diameter as visualized on coronary angiography [14]. Additionally, stenosis occurring within 5 mm outside the stent edge is also classified as ISR [15]. To determine the percentage of stenosis, the diameter of the lesion was compared with that of the normal segment of the proximal vessel using calipers (**Figure 2**).

Two angiographic projections at different angles were used to assess the percentage of stenosis. The posterior-anterior oblique view with cranial angulations and right anterior oblique view with caudal angulations were recommended for the left anterior descending artery (LAD). For the left circumflex artery (LCX), it was advised to use the right anterior oblique view with caudal angulations and posterior-anterior oblique view with caudal angulations. As for the right coronary artery (RCA), the left anterior oblique view and posterior-anterior oblique view with cranial angulations were suggested. Interventional cardiologists independently assessed each angiographic projection, selecting the more severe one to determine the percentage of stenosis. Previous and current angiographic images at the same angle were utilized for assessing the progression of identical lesions. Both previous and current angiography images were independently analyzed by two experienced interventional cardiologists. Quantitative coronary angiography and endovascular imaging techniques, such as IVUS, were additionally employed when the interventional cardiologists deemed the CAG image insufficient for analysis.

Baseline characteristic and laboratory testing

The baseline characteristics were collected, including gender, age, body mass index (BMI), and medical history. Hypertension was defined as a prior diagnosis of hypertension with medication treatment or repeated blood pressure measurements exceeding 140/90 mmHg after hospital admission [16]. Diabetes was defined as a prior diagnosis of diabetes with medication or insulin treatment, or in the absence of previous diabetes, a glycated hemoglobin level ≥6.5% during hospitalization [17]. Blood tests, including blood routine tests, liver and kidney function tests, cardiac enzyme spectrum analysis, lipid profile assessments, and glycated hemoglobin measurements were conducted prior to CAG. Blood samples were collected after a fasting period of 12 hours. Non-high-density lipoprotein cholesterol (non-HDL-C) was calculated by subtracting high-density lipoprotein cholesterol (HDL-C) from total cholesterol (TC). Low-density lipoprotein cholesterol (LDL-C) was determined using the Friedewald formula: LDL-C = TC - HDL-C - triglyceride (TG)/2.2 [18].

Statistical analysis

Continuous variables were presented as means ± standard deviation if they followed a normal distribution, or as medians and interquartile range (IQR) if they deviated from normality. Categorical variables were presented as percentages. The independent sample t-test was employed to compare continuous variables between two groups, while the Chi-squared test was used to compare categorical variables. The Pearson's chi-square test was utilized to assess the associations between two continuous variables and compare the constituent ratios. Variables with a significant *P*-value of less than 0.1 were included in the multivariate logistic regression model. Statistical signifi-

cance was defined as P<0.05. All statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Inc, Chicago, IL).

Results

Among the 510 patients enrolled in the study, 315 (61.8%) did not experience ISR or ANL, and were assigned to the Negative group. A total of 104 (20.4%) patients developed ISR and were classified into the ISR group, while 115 (22.5%) patients developed ANL and were assigned to the ANL group. It is worth noting that there was partial overlap between the ISR group and the ANL group, with 24 (4.7%) patients exhibiting both ISR and ANL simultaneously. The median follow-up duration for the two angiograms was 45 months (16-100 months).

Comparison between ISR group and Negative group

Four distinct types of DES were implanted in the previous angiography: durable polymer everolimus-eluting stent (DP-EES) such as PROMUS Element and XIENCE Xpedition; durable polymer sirolimus-eluting stent (DP-SES) such as Firebird and Firebird 2; zotarolimus-eluting stent (DP-ZES) such as Endeavor; and biodegradable polymer drug-eluting stent (BP-DES) such as SYNERGY, FIREHAWK, and Buma. The age of the ISR group was slightly higher than that of the Negative group, but the difference did not reach statistical significance. The groups did not differ significantly in terms of sex, BMI, current smoking or type of DES used. The proportion of hypertension was higher in the ISR group, but there was no statistically significant difference. The proportion of diabetes patients in the ISR group was significantly greater compared to that in the Negative group (39.7% in Negative group vs. 51.0% in ISR group, P=0.044). Similarly, the glycated hemoglobin (HbA1c) level was significantly higher in the ISR group compared to the Negative group (6.10% (5.80-6.80) in Negative group vs. 6.40% (5.88-7.40) in ISR group, P=0.026). Moreover, elevated serum creatinine (Scr) and uric acid (UA) levels were observed in the ISR group, with UA exhibiting a statistically significant difference between the two groups (333 umol/L (277-387) in Negative group vs. 352 umol/L (299-426) in ISR group, P=0.029). However, there were no statistically significant differences observed between the two groups for multiple lipid parameters, including TC, LDL-C, non-HDL-C, and ApoB (**Table 1**).

Comparison between ANL group and Negative group

There were no significant differences in age, gender, BMI, hypertension, and current smoking between the ANL group and the Negative group. Similarly, the proportion of diabetic patients was significantly higher in the ANL group compared to the Negative group (39.7% in Negative group vs. 51.3% in ANL group, P=0.031). Moreover, the ANL group exhibited a significantly elevated level of HbA1c compared to the Negative group (6.10% (5.80-6.80) in Negative group vs. 6.40% (6.00-7.30) in ANL group, P=0.005). Additionally, the ANL group exhibited higher levels of Scr and UA compared to the Negative group, with a statistically significant difference in Scr rather than UA between the two groups (71.0 umol/L (59.0-80.0) in Negative group vs. 74.0 umol/L (66.3-86.0) in ANL group, P=0.018). The corresponding calculated value of estimated glomerular filtration rate (eGFR) also showed a statistically significant difference between the two groups (91.93±23.73 ml/min/1.73 m^2 in Negative group vs. 86.79±22.85 ml/min/1.73 m^2 in ANL group, P=0.044). The difference in blood lipid levels between the two groups was notable, with higher levels of TC, LDL-C, and non-HDL-C observed in the ANL group compared to the Negative group; however, these differences did not reach statistical significance. The ApoB concentration was significantly higher in the ANL group than in the Negative group (68.0 mg/dL (57.0-78.0) in Negative group vs. 71.0 mg/dL (61.0-87.0) in ANL group, P=0.010) (**Table 1**).

Multivariate logistic regression model analysis

A multivariate logistic regression analysis was conducted to identify risk factors associated with the occurrence of ISR and ANL. The analysis included variables such as age, gender, BMI, hypertension, diabetes mellitus, current smoking, HbA1c, ALT, Scr, UA, eGFR, LDL, non-HDL-C, and ApoB.

In the analysis of risk factors for ISR, four variables, namely age, diabetes mellitus, HbA1c, and UA, showed a *p*-value of <0.1 in the uni-

Table 1. Characteristics of patients between ISR group, ANL group and Negative group

Parameters	Negative group (n=315)	ISR group (n=104)	*P* value Negative group vs. ISR group	ANL group (n=115)	*P* value Negative group vs. ANL group
Age, yrs	66.57±9.81	68.63±9.38	0.057	68.12±10.20	0.161
Sex, M/F	227/88	77/27	0.696	86/29	0.575
BMI, kg/m^2	24.38±2.99	24.17±3.01	0.544	24.36±3.25	0.940
HTN, n (%)	214 (67.9)	63 (60.6)	0.169	78 (67.8)	0.983
DM, n (%)	125 (39.7)	53 (51.0)	0.044	59 (51.3)	0.031
Current smoking, n (%)	55 (17.5)	19 (18.3)	0.851	20 (17.39)	0.987
HbA1c, %	6.10 (5.80-6.80)	6.40 (5.88-7.40)	0.026	6.40 (6.00-7.30)	0.005
ALT, U/L	19.0 (14.0-28.0)	18.5 (14.0-25.3)	0.429	20.5 (15.0-27.0)	0.467
Scr, umol/L	71.0 (59.0-80.0)	72.0 (62.0-88.0)	0.064	74.0 (66.3-86.0)	0.018
UA, umol/L	333 (277-387)	352 (299-426)	0.029	350 (296-409)	0.077
eGFR, (ml/min/1.73 m^2)	91.93±23.73	88.22±27.99	0.229	86.79±22.85	0.044
Types of DES			0.727		0.812
DP-EES	106 (33.7)	31 (29.8)		42 (36.5)	
DP-SES	63 (20.0)	26 (25.0)		21 (18.3)	
DP-ZES	29 (9.2)	9 (8.7)		13 (11.3)	
BP-DES	117 (37.1)	38 (36.5)		39 (33.9)	
Cholesterol level					
TC, mmol/L	3.50 (3.01-3.96)	3.40 (3.02-3.99)	0.653	3.58 (3.11-4.29)	0.100
TG, mmol/L	1.26 (0.89-1.76)	1.17 (0.88-1.68)	0.188	1.28 (0.87-1.69)	0.626
HDL-C, mmol/L	1.07 (0.92-1.28)	1.08 (0.95-1.28)	0.724	1.06 (0.88-1.19)	0.121
LDL-C, mmol/L	1.78 (1.41-2.13)	1.73 (1.42-2.09)	0.804	1.89 (1.51-2.42)	0.055
Non-HDL-C, mmol/L	2.39 (1.96-2.83)	2.29 (1.86-2.73)	0.315	2.45 (2.07-3.27)	0.060
ApoA, mg/dL	1.22 (1.09-1.35)	1.25 (1.11-1.36)	0.769	1.22 (1.08-1.35)	0.383
ApoB, mg/dL	68.0 (57.0-78.0)	66.0 (57.0-80.8)	0.813	71.0 (61.0-87.0)	0.010
Lpa, mg/dL	17.5 (10.1-39.3)	17.4 (10.4-80.8)	0.330	19.6 (9.9-41.6)	0.505
Follow-up time, month	44.0 (16.0-102.0)	48.0 (17.0-107.0)	0.634	54.0 (14.0-108.0)	0.175

ISR: in-stent restenosis; ANL: aggravated non-intervened coronary lesion; F: female; M: male; BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; HbA1c: glycated hemoglobin; ALT: alanine transaminase; Scr: serum creatinine; UA: uric acid; TC: total cholesterol; eGFR: estimated glomerular filtration rate; DES: drug-eluting Stent; DP-EES: durable polymer everolimus-eluting stent; DP-SES: durable polymer sirolimus-eluting stent; DP-ZES: zotarolimus-eluting stent; BP-DES: biodegradable polymer drug-eluting stent; TC: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; ApoA: apolipoprotein A; ApoB: apolipoprotein B; Lpa: lipoprotein a.

Table 2. Multivariable logistic analysis for the risk factors of ISR

Variable	OR	95% CI		P
A: Variables with P<0.1				
Age	1.019	0.997	1.043	0.094
DM	1.457	0.946	2.245	0.088
HbA1c	1.197	0.999	1.434	0.051
UA	1.003	1.000	1.005	0.032
B: After the stepwise selection using *P* value (until P<0.05)				
HbA1c	1.229	1.022	1.477	0.028
UA	1.003	1.000	1.005	0.024

ISR: in-stent restenosis; OR: odds ratio; CI: confidence interval; DM: diabetes mellitus; HbA1c: glycated hemoglobin; UA: uric acid.

variate logistic analysis. Stepwise regression was employed to identify risk factors for the multivariable model. Consequently, HbA1c (OR 1.229, 95% CI 1.022-1.477, P=0.028) and UA (OR 1.003, 95% CI 1.000-1.005, P=0.024) were found to be independent risk factors for ISR (**Table 2**).

The univariate logistic analysis for the assessment of risk factors associated with ANL identified ten variables with a *p*-value <0.1, including diabetes mellitus, HbA1c, Scr, UA, eGFR, TC, HDL-C, LDL-C, non-HDL-C, and ApoB. After conducting stepwise regression analysis to identify the risk factors for our multivariable model, we found that HbA1c (OR 1.215,

Table 3. Multivariable logistic analysis for the risk factors of ANL

Variable	OR	95% CI		P
A: Variables with P<0.1				
DM	1.500	0.988	2.275	0.057
HbA1c	1.279	1.075	1.523	0.006
Scr	1.009	1.002	1.016	0.013
UA	1.002	1.000	1.004	0.099
eGFR	0.992	0.983	1.001	0.067
TC	1.271	1.000	1.616	0.050
HDL-C	0.510	0.231	1.126	0.096
LDL-C	1.397	1.035	1.886	0.029
Non-HDL-C	1.313	1.038	1.661	0.023
ApoB	1.017	1.005	1.028	0.003
B: After the stepwise selection using *P* value (including ApoB) (until P<0.05)				
HbA1c	1.215	1.010	1.460	0.039
Scr	1.007	1.003	1.017	0.009
ApoB	1.017	1.006	1.029	0.004
C: After the stepwise selection using *P* value (excluding ApoB) (until P<0.05)				
HbA1c	1.240	1.034	1.487	0.020
Scr	1.009	1.002	1.016	0.008
Non-HDL-C	1.339	1.053	1.704	0.017

ANL: aggravated non-intervened coronary lesion; OR: odds ratio; CI: confidence interval; DM: diabetes mellitus; HbA1c: glycated hemoglobin; UA: uric acid; TC: triglyceride; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; ApoB: apolipoprotein B.

95% CI 1.010-1.460, P=0.039), Scr (OR 1.007, 95% CI 1.003-1.017, P=0.009), and ApoB (OR 1.017, 95% CI 1.006-1.029, P=0.004) emerged as independent risk factors associated with ANL. However, due to the potential challenges in detecting ApoB concentration in many healthcare facilities, further analysis was conducted to identify the risk factors in the absence of ApoB data. The results revealed that HbA1c (OR 1.240, 95% CI 1.034-1.487, P=0.020), Scr (OR 1.009, 95% CI 1.002-1.016, P=0.008), and non-HDL-C (OR 1.339, 95% CI 1.053-1.704, P=0.017) were identified as the independent risk factors of ANL (**Table 3**).

Comparison between ISR only group and ANL only group

After excluding 24 patients who exhibited both ISR and ANL, there were 80 participants in the ISR only group and 91 participants in the ANL only group. Further comparison of these two groups revealed no significant differences in age, gender, BMI, hypertension, diabetes mellitus, current smoking, liver and kidney function and follow-up time (**Table 4**). However, distinct distributions of several lipid levels were observed between the two groups. Although not statistically significant, TC (3.36 mmol/L (2.92-3.76) in ISR only group vs. 3.56 mmol/L (3.10-4.30) in ANL only group, P=0.060) and LDL-C (1.69 mmol/L (1.36-2.02) in ISR only group vs. 1.83 mmol/L (1.49-2.42) in ANL only group, P=0.053) were higher in the ANL only group compared to the ISR only group; HDL-C levels were lower in the ANL only group compared to the ISR only group (1.10 mmol/L (0.97-1.30) in ISR only group vs. 1.05 mmol/L (0.88-1.22) in ANL only group, P=0.085). In contrast, non-HDL-C (2.17 mmol/L (1.81-2.66) in ISR only group vs. 2.44 mmol/L (2.03-3.27) in ANL only group, P=0.007) and ApoB (63.5 mg/dL (56.0-73.0) in ISR only group vs. 71.0 mg/dL (61.0-87.0) in ANL only group, P=0.011) levels were significantly higher in the ANL only group than in the ISR only group (**Figure 3**).

Discussion

The study results indicate that ISR and ANL are associated with distinct risk factors, indicating potential differences in plaque formation between stented vessels and non-intervened vessels. This study provides novel insights for clinicians regarding the management of risk factors. The main findings of the study can be summarized as follows: (i) both blood glucose levels and chronic kidney disease are established risk factors for both ISR and ANL; (ii) elevated levels of blood lipids, including LDL-C, non-HDL-C, and ApoB, exhibit a stronger association with the progression of ANL rather than ISR; and (iii) in patients undergoing long-term statin treatment after PCI with non-intervened coronary lesions, the concentration of non-HDL-C and ApoB plays a crucial role in risk assessment.

The aim of this study was to analyze and compare the differential impacts of identical risk factors on ISR and ANL under controlled conditions. To achieve this aim, we recruited a unique patient population with multiple lesions, including both stented and non-intervened coronary lesions. This study design, similar to

Table 4. Characteristics of patients between ISR only group and aggravated non-intervened lesion only group and Negative group

Parameters	ISR only group (n=80)	ANL only group (n=91)	P
Age, yrs	68.34±8.94	67.73±10.04	0.674
Sex, M/F	56/24	65/26	0.838
BMI, kg/m^2	24.09±2.89	24.33±3.21	0.608
HTN, n (%)	47 (51.6)	62 (68.1)	0.203
DM, n (%)	38 (41.8)	44 (48.4)	0.911
Current smoking, n (%)	13 (14.3)	14 (15.4)	0.877
ALT, U/L	17.0 (15.0-25.0)	20.0 (15.0-27.0)	0.849
Scr, umol/L	69.0 (60.0-87.0)	74.0 (65.5-85.0)	0.506
UA, umol/L	345 (299-413)	344 (297-383)	0.723
eGFR, (ml/min/1.73 m^2)	90.28±29.15	88.25±22.78	0.619
HbA1c, %	6.30 (5.80-7.10)	6.30 (6.00-7.13)	0.585
Cholesterol level			
TC, mmol/L	3.36 (2.92-3.76)	3.56 (3.10-4.30)	0.060
TG, mmol/L	1.17 (0.88-1.65)	1.28 (0.87-1.66)	0.112
HDL-C, mmol/L	1.10 (0.97-1.30)	1.05 (0.88-1.22)	0.085
LDL-C, mmol/L	1.69 (1.36-2.02)	1.83 (1.49-2.42)	0.053
Non-HDL-C, mmol/L	2.17 (1.81-2.66)	2.44 (2.03-3.27)	0.007
ApoA, mg/dL	1.27 (1.13-1.39)	1.22 (1.08-1.35)	0.296
ApoB, mg/dL	63.5 (56.0-73.0)	71.0 (61.0-87.0)	0.011
Lpa, mg/dL	16.0 (9.9-42.6)	19.6 (8.4-36.9)	0.770
Follow-up time, month	45.0 (16.0-95.0)	48.0 (13.0-96.0)	0.706

ISR: in-stent restenosis; ANL: aggravated non-intervened coronary lesion; F: female; M: male; BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; ALT: alanine transaminase; Scr: serum creatinine; UA: uric acid; HbA1c: glycated hemoglobin; TC: total cholesterol; TC: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; ApoA: apolipoprotein A; ApoB: apolipoprotein B; Lpa: lipoprotein a.

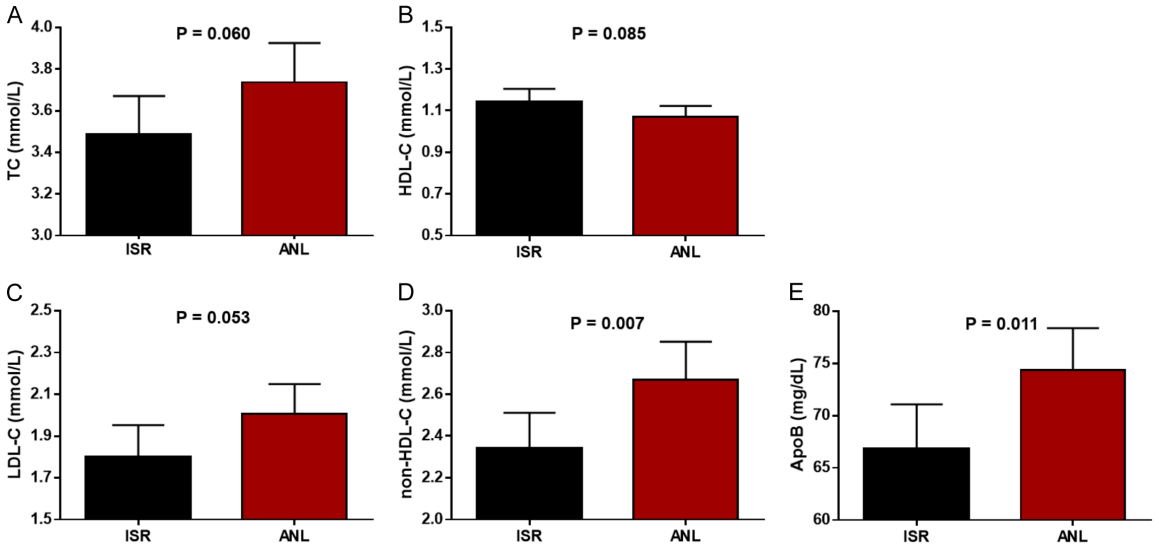

Figure 3. TC, HDL-C, LDL-C, non-HDL-C and ApoB between ISR only group and ANL only group. A: TC between two groups; B: HDL-C between two groups; C: LDL-C between two groups; D: non-HDL-C between two groups; E: ApoB between two groups. ISR: in-stent restenosis; ANL: aggravated non-intervened coronary lesion; TC: total cholesterol; TC: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; ApoB: apolipoprotein B.

"twin coronary lesions", helps mitigate potential experimental biases to some extent. The progression of atherosclerosis in coronary arteries occurs gradually over time. Previous studies have demonstrated that the 5-year incidence rates of both ISR and ANL are approximately 20% [8-11]. The median follow-up duration for the ISR group was 48 months (17-107 months), while the ANL group had a median follow-up duration of 54 months (14-108 months). However, it is important to note that this retrospective study included patients who underwent reexamination due to recurrent angina symptoms, positive treadmill exercise test, or coronary CTA revealing moderate to severe stenosis. Consequently, the incidence rates of ISR and ANL were higher in the study population compared to those observed in the general population. In our study, the incidence rates of ISR and ANL were 20.4% and 22.5%, respectively.

Previous studies have demonstrated the association between diabetes, hypertension, smoking, chronic kidney disease, and CAD [19-21]. HbA1c serves as an evaluation index of blood glucose level, reflecting the average blood glucose level of patients over the past three months [17]. In line with previous research, our study results indicate that HbA1c is an independent risk factor for both ISR and ANL [22-24]. The results of this study did not demonstrate a significant correlation between hypertension and CAD, potentially attributed to the effective control of blood pressure through the administration of antihypertensive medications and the absence of long-term blood pressure monitoring indicators. Furthermore, all patients received comprehensive smoking cessation training after PCI, thereby limiting the representation of current smokers as a potential risk factor. Chronic kidney disease is a major risk factor for CAD [25]. The impact of UA on CAD, including coronary artery calcification, has also been highlighted in many studies [26, 27]. In this study, Scr emerges as an independent risk factor for ANL, while UA emerges as an independent risk factor for ISR. However, it should be noted that Scr and UA exhibit a strong correlation in this study ($r=0.348$, $P<0.001$). Moreover, when comparing the ISR only group with the ANL only group, no significant differences were observed in either Scr or UA levels. Consequently, determining whether these two factors exert varying degrees of influence on ISR and ANL remains challenging, and further research is necessary to elucidate this matter.

Blood lipid levels have always been an important factor affecting coronary atherosclerosis, and pharmacological intervention targeting dyslipidemias is acknowledged as one of the most effective strategies to impede the progression of coronary atherosclerosis [12]. According to the 2019 ESC/EAS Guidelines for the management of dyslipidemias, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended for primary prevention in individuals at very high risk [18]. In this study, patients were required to adhere to long-term statin therapy and regularly monitor their blood lipids. Although all patients exhibited relatively low blood lipid levels, some individuals still failed to meet the standard for LDL-C levels.

The present study did not find any significant correlation between blood lipid levels (including TC, HDL-C, LDL-C, non-HDL-C, and ApoB) and ISR, which is inconsistent with the results of previous studies [28-30]. However, this does not imply that blood lipids do not exert an impact on the vessels after stenting. Notably, a significant difference in blood lipid levels was observed when comparing the ANL only group to the ISR only group. This result suggests that patients with elevated blood lipid levels are more likely to exhibit ANL rather than ISR. The selection criterion for undergoing CAG testing in this study was the occurrence of angina in patients. Both ISR and ANL are potential etiologies of angina, and patients with dyslipidemias may seek medical attention earlier due to angina caused by ANL. This phenomenon is intriguing and significant, yet a comprehensive mechanism to explain this conclusion remains elusive. Different mechanisms contribute to the development of ISR, including biological or patient-related factors, anatomic factors, procedural factors, and stent factors [31, 32]. The ISR group had a median follow-up duration of 48 months (17-107 months), indicating that ISR events in this study were primarily attributed to neointimal hyperplasia [31, 33]. Blood lipid levels have a relatively minor impact on the formation of neointimal hyperplasia induced by hypersensitivity and inflammatory reac-

tions [33]. Moreover, the favorable intravascular environment following DES implantation (including drugs used in the stent and a larger lumen diameter compared to existing plaques) may confer improved resistance against blood lipid levels. Further research is warranted to investigate this phenomenon.

ApoB is present in every particle of very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, LDL, and Lp(a). The plasma ApoB level corresponds to the total count of ApoB particles. The quantity of ApoB particles that infiltrate and accumulate in the arterial wall primarily depends on the number of ApoB particles in the arterial lumen [34]. Consequently, ApoB has the potential to serve as a more effective indicator of blood lipid level [35, 36]. However, the detection of ApoB concentration presents intricacies and challenges in many healthcare facilities. Additionally, LDL-C, non-HDL-C, and ApoB concentrations are highly correlated [37, 38]. Therefore, ApoB is currently not utilized as the primary marker for blood lipid observation.

Previous studies have indicated that measurement of LDL-C results may not accurately reflect the patient's blood lipid levels in patients with elevated TG levels, diabetes, obesity, or very low achieved LDL-C levels [35, 39, 40]. In this study, the patients received statin treatment and maintained relatively low blood lipid levels. At the same time, a relatively high proportion of diabetes was observed in this study (43.5%). Consequently, in this population, LDL-C may not accurately reflect the patient's blood lipid levels. The 2019 ESC/EAS Guidelines for the management of dyslipidemias also recommend evaluating non-HDL-C and ApoB for risk assessment, particularly in individuals with high TG levels, diabetes, obesity, or very low LDL-C levels [18]. In the results of this study, ApoB emerged as an independent risk factor for ANL. However, considering the challenges in detecting ApoB in many healthcare facilities, we further conducted a multivariate logistic regression analysis when obtaining ApoB concentration was not feasible. The results indicated that when excluding the measurement value of ApoB, non-HDL-C rather than LDL-C emerged as an independent risk factor for ANL. Therefore, in patients with non-intervened coronary lesions and long-term oral statin treatment after PCI, prioritizing the control of ApoB levels is recommended. In healthcare facilities where ApoB concentration is not available, non-HDL-C should be utilized as the primary detection indicator.

Limitations

1) This study is a retrospective study that enrolled patients who underwent reexamination due to recurrent angina symptoms, positive treadmill exercise test, or coronary CTA revealing moderate to severe stenosis. It is important to acknowledge potential biases in patient selection. 2) The study population was limited to a single center, thus the generalizability of the conclusions to broader populations is uncertain. Further multi-center prospective studies are necessary. 3) The LDL-C levels of the study population did not completely reach the recommended cholesterol (LDL-C) reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L, as outlined in the 2019 ESC/EAS Guidelines for the management of dyslipidemias. 4) The assessment of ISR and ANL in this study primarily relied on angiographic images. The low use rate of quantitative coronary angiography and intravascular ultrasound in this study may introduce potential inaccuracies.

Conclusions

In patients with non-intervened coronary lesions after stenting: Both ISR and ANL are influenced by blood glucose levels and chronic kidney disease. Moreover, non-intervened coronary lesion is more significantly affected by blood lipid levels, including TC, LDL-C, non-HDL-C, and ApoB. Therefore, closely monitoring ApoB and non-HDL-C levels is imperative for this patient population.

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Disclosure of conflict of interest

None.

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